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Measurement of Side Effects of Drugs

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Summary

In a clinical trial of two antirheumatic agents two methods of collection of side effects were used, one with and the other without a check list of possible symptoms. Findings suggested that the use of a check list interfered with the collection of side effects. Known side effects of aspirin—tinnitus, deafness, and gastrointestinal disturbance—were more efficiently shown and symptoms not included in the check list were more likely to be reported when a check list was not used.

Introduction

Though considerable importance now attaches to the early recognition of drug toxicity the amount of research effort devoted to methods of detection of adverse effects of drugs is very small in comparison with that spent on measurement of effectiveness. The insistence by some authorities that a check list should be used to remind patients taking part in clinical trials of symptoms they might be having is presumably based on domestic principles; the housewife can hardly be expected to remember her household requirements without a shopping list. It is well known to a grocer that if his wares are displayed they are more likely to be bought. The same is true of side effects. Greenblatt (1964) showed that side effects were about five times more frequent if a check list was used. The housewife knows, however, that a display of wares in the supermarket is not always desirable; she may select more goods but forget some that she needed. The possibility that the same could be true of side effects prompted this investigation.

Methods

A study of methods of collection of side effects was made as part of a six-month assessment of two analgesic antiinflammatory drugs, aspirin and fenoprofen, the results of which were reported by Huskisson *et al.* (1974). Sixty patients with rheumatoid arthritis at two centres received either aspirin or fenoprofen according to a randomized schedule. At one centre patients were simply asked the following question: "Have you noticed any new symptoms which might be related to the treatment?" At the other centre a check list was also used comprising a list of 21 possible side effects including tinnitus, deafness, and a

variety of gastrointestinal complaints as well as a number of side effects with no obvious relevance. Each side effect was recorded as absent, slight, moderate, or severe and assigned values of 0, 1, 2, or 3 respectively; from the sum of the values obtained a side effect score was calculated.

Results

Auditory and gastrointestinal side effects were significantly commoner on aspirin than on fenoprofen. The remainder of the side effects elicited occurred with equal frequency on both drugs and were called "irrelevant." These three groups are shown in table I according to whether or not a check list was used. The group in which no check list was used proved to be more efficient in detecting the two significant groups of side effects. For both auditory and gastrointestinal side effects the incidence on fenoprofen was at least twice as great when a check list was used, and the incidence on aspirin was not correspondingly greater. Thus the difference between the incidence of the significant side effect and the "background" incidence in the control population was diminished. This was particularly apparent for gastrointestinal disturbances, which presumably reflected the frequent occurrence of such symptoms unrelated to treatment.

Irrelevant side effects were much commoner when a check list was used (see table I). It could be argued that a check list should be used so that the occasional totally unexpected side effect will be reported. That this is not so is shown in table II. While side effects which appeared on the check list (solicited side effects) were much more frequently reported when a check list was used, unsolicited side effects (those which did not appear on the check list) were more likely to be volunteered when a check list was not used. A check list did not much increase the rate of appearance of side effects (see fig.)

TABLE I—Side Effect Scores (%) *for Three Groups of Side Effects, collected either in Response to Simple Question or with Check List of possible Symptoms

Side Effect	Treatment	Side Effect Score (%)	
		Check List	No Check List
Deafness and tinnitus	Aspirin	111	91
	Fenoprofen	9	3
Gastrointestinal ..	Aspirin	93	134
	Fenoprofen	54	26
"Irrelevant"	Aspirin	143	87
	Fenoprofen	130	68

*Side effect score (%) was calculated by multiplying total side effect score for each patient by 100 and dividing by number of patients

TABLE II—Side Effect Scores (%) according to whether Side Effects were included on Check List (Solicited) or not (Unsolicited)

Side Effects	Side Effect Score %	
	Check List	No Check List
Solicited	239	126
Unsolicited	33	65

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Cumulative number of patients (expressed as percentage of total number complaining) with gastrointestinal or auditory side effects due to aspirin therapy.

Discussion

The results of this study confirm the finding of Greenblatt (1964) that side effects are more likely to be elicited if a check list is used. They also suggest that relevant side effects are more likely to be detected if a check list is not used. The check list is most likely to interfere with the collection of symptoms which occur frequently even in the absence of drug therapy. This is illustrated by the incidence of gastrointestinal disturbance in the study. Many people, and especially patients with rheumatoid arthritis, suffer minor gastrointestinal irregularities and if prompted by a check list will volunteer these as potential drug induced side effects.

The evidence also suggests that the totally unexpected side effect of a drug is more likely to be detected when a check list is not used. If this side effect is included in the check list its apparent incidence will be reduced by reports of its occurrence in the control group; if it is not included in the check list it is less likely to be reported.

It is well known that side effects occur on placebo therapy just as symptoms occur in normal people. This phenomenon is a nuisance in the detection of side effects of drugs. Since check lists increase the incidence of irrelevant complaints they should not be used.

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Propranolol in the Treatment of Migraine

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Summary

Beta-blocking drugs that prevent cranial vasodilatation are potentially valuable in the prophylaxis of migraine. Forty-nine patients with either classic or common migraine were treated with propranolol 160 mg/day for an average of six months. The first 30 of the patients to respond well to this treatment then participated in a double-blind cross-over trial with a placebo and propranolol. The mean frequency of headache attacks was significantly reduced by propranolol. None of the patients expressed a preference for placebo. Propranolol seems to be an effective prophylactic for common and classic migraine but the antimigraine properties of the various beta-blocking agents probably differ.

Introduction

The intensity of migraine is closely related to the amount of dilatation of the extracranial arteries (Wolff, 1963) and the vessels of the bulbar conjunctiva (Piovella, 1972). Furthermore,

migraine is alleviated by agents which produce cranial vasoconstriction. Falck *et al.* (1968) showed that the vessels of the pia mater contain both alpha- and beta-adrenergic receptors and that beta-blocking agents may affect the cerebral blood flow. That beta-blocking agents are potentially of value in the treatment of migraine headache has been proved empirically (Rabkin, 1966; Bekes *et al.*, 1968; Wykes, 1968; Lund-Larsen, 1969; Wideroe, 1969) and by controlled trials (Weber and Reinmuth, 1971; Malvea *et al.*, 1973). Ekblom and Lundberg (1972) and Sjaastad and Stensrud (1972), however, found that pindolol had no significant antimigraine effect.

The aim of this study was to investigate the value of propranolol in preventing attacks of migraine.

Patients and Methods

We asked doctors in the region to refer to us all patients suffering from migraine who might benefit from prophylactic treatment. Altogether we examined about 100 patients. Forty-nine (44 women and five men) were diagnosed as having either "classic" or "common" migraine (Ad Hoc Committee, 1962). Their ages ranged from 18 to 55 years with an average of 40 years. All except four patients had two or more attacks a month. They were all treated as outpatients. All had been taking antimigraine drugs, in most cases with some benefit.

Each of the 49 patients was entered in a pilot study in which for a period averaging six months (range 2-24 months) they were given propranolol 40 mg by mouth four times daily. Attacks were treated by the usual antimigraine drugs. The patients kept a record of the frequency, intensity, and duration of their

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