CONTINUED USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: AN INDEX OF CLINICAL EFFICACY

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1 A double-blind entry to a trial of an active non-steroidal anti-inflammatory drug, flurbiprofen against placebo was undertaken until 100 patients with classical rheumatoid arthritis had been allocated to each treatment.

2 Each patient was given a long-term supply of drug and was asked to vary their own dosage within simple limits, according to the severity of their symptoms. They were instructed to return immediately they felt dissatisfied with their medication either on account of side-effect or of lack of effect.

3 The length of time that patients remained satisfied with their drug was used as the sole measure of efficacy of the drug. At 2 weeks there were only 30% remaining on placebo and by 4 months no patients remained satisfied with the inactive drug. Forty-three per cent were satisfied with flurbiprofen at the end of 1 year.

4 Clearly compliance with anti-rheumatic drugs is better if the drugs are effective and there is no long-term placebo response in rheumatoid arthritis.

Introduction

It is well recognized that over the long term, continued use of prescribed antirheumatic drugs is not good (Geersten, Gray & Ward, 1973) and that current standard methods of assessment of the efficacy of these agents largely suffer from the short duration of therapy which is used (Lee, Sturrock, Kennedy & Dick, 1973). The current study was undertaken to test the hypothesis that continued long term use can itself be useful as an index of efficacy of anti-inflammatory drugs.

Methods

Two hundred patients with classical rheumatoid arthritis (Ropes, 1959) volunteered to participate in this study. These patients comprised 43 male and 157 female patients whose age ranged from 22–71 years (mean $\pm$ s.e. mean 58 ± 3.1 years). Each patient had early disease without complications and no patient had sufficiently severe disease to justify the use of second line drugs.

In no patient was there a contraindication to the prescription of flurbiprofen. Flurbiprofen is an effective antirheumatic drug of the propionic acid series (Dick, 1978).

Trial design

Each patient was randomly allocated in a double blind fashion to flurbiprofen capsules (25 mg) or to identical placebo capsules. Each was instructed using precisely the same words to take the minimum number of capsules sufficient to control their symptoms and to vary the dose in proportion to these symptoms. Each patient was instructed to return immediately if any untoward effect was noted or if, at the highest permitted dose (12 capsules/day) symptoms were not relieved. All patients were furnished with telephone numbers whereby they could contact one of the study physicians 24 h per day (PJR or WCD). Otherwise each patient was reviewed routinely at three monthly intervals by physicians not concerned in the study. On three occasions during the first year of the study, patients were contacted without prior warning to ensure continued use of their drugs.

On two occasions, every patient was reviewed and placebo capsules were substituted for the trial preparation. The patients were unaware of the substitution and the placebo was continued for as long as was tolerable to the patient. In this event, their instruction was to resume their previous capsules. The reviewer on these occasions had no previous and no subsequent contact with the study.

Figure 1 'Compliance' with flurbiprofen (● patients taking flurbiprofen; ○ patients taking placebo).

Assessment of result

Continued patient satisfaction with and use of their prescribed drug was taken as the sole arbiter of efficacy in this study. Considerable care was taken to explain to each patient that they were the best judge of their own symptoms, and as long as they maintained or improved their functional status the purpose of therapy was being fulfilled.

Results

The results of this study are illustrated in Figure 1. It can be seen that patient numbers diminish rapidly with time when placebo was presented. At the end of 2 weeks, approximately 30% of the original 100 patients remained satisfied with placebo while at 1 month only 5% remained in this category. On the other hand, the dropout rate when flurbiprofen was prescribed was much slower and 43% of the patients remained satisfied with their medication after one year.

The early dropouts in the flurbiprofen group were approximately equally divided between those dropping out because of side effects and those dropping out for lack of effect.

6% of all the patients included proved to be incapable of understanding and following the instructions and are not included in the final analyses. The majority of these proved to be illiterate. At the two review periods for placebo capsules all patients later proved to have been receiving active drug and all reverted on each occasion to their original capsules within 2 weeks.

Discussion

Whether or not a patient will comply with their physician's instructions and take prescribed

medication is an important and complex question. Compliance is a function of patient motivation and intelligence and it is this aspect of the problem which is usually stressed (Ayd, 1974). It is also a function of the physician's ability to communicate and the results of the present study show that in 6% of patients, there was total failure in this aspect, despite that fact that this was central to the entire programme and considerably more time was devoted to explanation and instruction than could ever be allocated on a routine basis. With such patients, it is necessary to resort to frequent medical supervision and if possible to enlist the assistance of family members.

Compliance is also a function of the therapeutic ratio of the drug in question. Where a drug has a pronounced and immediate effect, as does Lomotil in the treatment of diarrhoea, then compliance is likely to be good. On the other hand, where a drug has a delayed action, produces side effects and possesses an efficacy, which is less dramatic such as in the treatment of hypertension or depression, compliance is likely to be more of a problem. It has been stated that 'compliance with antirheumatic drugs is not good' (Geersten *et al.*, 1973). The results of the present study strongly refute this statement. Both unexpected checking and placebo pulse studies have demonstrated clearly that the patients in this study were continuing to use their prescribed medication. The clue to this apparent contradiction lies in the instructions given to the patients in this study. Non-steroidal antirheumatic first line drugs are symptomatic remedies. If they do not relieve individual patient's symptoms then there is no justification for prescribing them and again if they produce more intolerable side effects than their degree of efficacy warrants they should not be prescribed. Provided that they do relieve symptoms without producing side effects, then the patient will most certainly continue to use the drugs and the results of this study clearly show this to be the case. It is of considerable interest that since completing this study, flurbiprofen has been withdrawn from the Centre for Rheumatic Diseases in Glasgow. Almost without exception long term responding patients on being withdrawn have suffered an exacerbation of symptoms and have had considerable difficulty in transferring to another non-steroidal antirheumatic drug.

In only one instance did any patient exceed the prescribed maximum dose and this was through a misunderstanding of our instructions. This patient continued to use this increased dose without side-effects for the full period of the study.

This study was designed to explore the question 'can continued patient satisfaction be used as an index of the efficacy of antirheumatic drugs?' A great deal of attention has been directed towards devising more and more complex evaluation programmes based upon short or long term single or double-blind structures. Considerable effort has been directed toward devising

more and more complex subjective, 'semisubjective' and objective methods of assessment (Lee *et al.*, 1973; Levy & Dick, 1976). In no instance using any combination of the above techniques have such clear cut differences between active agent and placebo been produced. Clearly further work is required to explore this method in the context of comparative drug evaluation and this is in progress.

It is obvious from the results of this study that our present thoughts upon placebo responses require re-evaluation. It is stated frequently that about one-third of patients with rheumatoid arthritis are 'placebo reactors'. This in itself is an extrapolation of the work of Beecher (1959) and Lasagna *et al.* (1954), who did document a proportion of placebo reactors but the duration of most of their studies was brief. Indeed, our own results mirror their data that at two weeks approximately one-third of patients were still continuing to use placebo. What has not been clearly stated in the literature is that the placebo effect is transitory and indeed there is virtually no such thing

as a long term placebo responding rheumatoid arthritis patient. The results of this study are in this respect in total disagreement with a single previous report (Traut & Passarelli, 1957) and we have no explanation for this. It is important to note, however, that the patient material was fully characterized in the present study and all patients had sero-positive erosive inflammatory symmetrical polyarthritis. In addition, all had symptoms which would be relieved by anti-rheumatic drugs, i.e. all had an element of reducible disease.

In conclusion, the results of this study demonstrate that using continued patient satisfaction alone as a method of assessment, clear cut differences between placebo and an active antirheumatic drug can be demonstrated. Responding patients comply with physicians' instructions when an effective and tolerated symptomatic remedy is presented and there is no such thing as a sustained placebo response in rheumatoid arthritis.

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