Br. J. clin. Pharmac. (1976), 3, 331-332

HOW DOUBLE BLIND IS DOUBLE BLIND? AND DOES IT MATTER?

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1 In an apparently double blind crossover study, two experienced measurement technicians were able to identify many of the treatment periods.

2 They most often correctly identified aspirin, a drug with prominent effects and side effects.

3 It is argued that in many circumstances it is better to use a blind observer who is not concerned with the giving of treatment or the collection of side effects.

Introduction

Changes in medical practice are not made in decisive steps. Rather the pendulum swings, its middle point reflecting the changes, but the extremes of its traverse determined by the first enthusiasm of discovery and the subsequent reaction. So with clinical trials, the revolution in which double blind, controlled studies replaced the experience of great physicians as a guide to therapy has been followed by the realization that such studies can also be fallacious. In this paper, we present evidence that double blind trials may not be double blind and suggest that there are situations in which double blind trials may be misleading and should be avoided.

Methods

Eighteen patients with definite or classical rheumatoid arthritis by the A.R.A. criteria took part in a crossover trial comparing aspirin (3.6 g daily), a new anti-inflammatory agent, not at present available in Britain at the time of writing, and placebo. Each treatment was given for 2 weeks. All treatments were supplied in identical capsules.

Two experienced measurement technicians made routine clinical measurements and recorded side effects at the end of each week. After the assessment, and again when the study had been completed, the technicians were asked to guess which treatment the patient had been receiving, and to state their reasons.

Results

Sixteen patients completed the study, providing forty-eight treatment periods and sixteen complete sequences. The identification rates are shown in Table 1; such high rates are very unlikely to have occurred by chance. Table 2 shows that aspirin was more likely and the unknown drug less likely to be correctly identified. Reasons for identification are shown in Table 3.

Discussion

It is the observer who should be kept in ignorance of the nature of a treatment being assessed; the patient is unlikely to be biased unless he is given a treatment which he recognizes. If the observer becomes aware of the nature of the treatment, the major purpose of the double blind technique is therefore lost.

The observer may become aware of the nature of a treatment when that treatment has characteristic effects or characteristic side effects. A treatment may be recognized by the action which is being measured; it might not matter, for instance, if a treatment was so obviously effective that the observer could immediately identify it. But other aspects of the effect may provide the same information: for example, a drug might be recognized by a particularly fast or slow action. When side effects readily identify a treatment such as aspirin, it is better to use single blind methodology and ensure that blindness is maintained by having a separate observer to elicit side effects. This technique has been successfully used in a long term trial of penicillamine and gold, the former with recognizable side effects, the latter given by injection (Huskisson, Gibson, Balme, Berry, Burry, Grahame, Hart, Henderson & Wojtulewski, 1974).

There are other situations where double blind trials are difficult and may be misleading. These include comparisons of drugs of different

Table 1 Identification rate for individual treatment periods and complete treatment sequences, based on questioning after each assessment and again upon completion of the whole study.

	After each assessment	*Upon completion of the study*
Treatment period	21(44%)	33(68%)
Treatment sequence	3(19%)	9(56%)

Table 2 Identification rate for individual treatments based on questioning upon completion of the study.

Treatment	*Identification rate*
Aspirin	81%
Test anti-inflammatory drug	56%
Placebo	69%

Table 3 Reasons for correct identification of treatment periods upon completion of the study.

Reason for identification	*Number*
Side effects	5
Effectiveness	10
Placebo relapse	9
Guesswork/Exclusion	9

appearance, those with different dosage schedules and those given by different routes. It is unnecessary, as well as unkind, to give placebo injections to the control group in a trial of an injectable preparation if assessments can be made by a blind observer. Similarly, it is unnecessary to use complicated double placebo techniques, sometimes requiring large numbers of pills to be taken. The giving of large numbers of placebo tablets, placebo injections or placebo tablets of a particular colour may alter the response and introduce a further variable. For example, the effects of placebo are altered by changes of colour, but this phenomenon is not observed with active analgesics (Huskisson, 1974). Injections have a greater placebo effect than tablets (Traut & Passarelli, 1957), and the placebo effect may be increased by increasing the number of tablets prescribed. In many trials, double blindness is unnecessary, and in some it is actually misleading.

It has been routine practise in trials carried out at the London Hospital to ensure the maintenance of double blindness in trials by asking the physician to guess which treatment a patient is receiving (Mason, 1975, personal communication). In a trial of immunosuppressives and gold, treatment was correctly identified in only two of one-hundred and twenty-one patients (Currey, Harris, Mason, Woodland, Beveridge, Roberts, Vere, Dixon, Davies & Owen-Smith, 1974); it is difficult to imagine that such a low rate of identification would be achieved in trials of drugs with more characteristic side effects such as D-penicillamine.

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(Received July 24, 1975)