For Debate

Controlled trials in single subjects

1 Value in clinical medicine

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Randomised controlled group trials are the gold standard in clinical research and provide information about the average effect of a treatment in a target population. Such information, however, cannot necessarily be transferred to a single patient because finding a significant effect of treatment does not mean that all the study subjects responded. Besides, in real life clinicians are often confronted with vague symptoms and poorly defined diseases; this is a different case from the strict criteria used in scientific studies. In an attempt to adapt the general knowledge about a new treatment to a particular patient the clinician tries out drugs. Such an uncontrolled trial and error approach is, however, often biased towards a false positive effect as most disorders are self limiting, the placebo effect may be appreciable, and the patient is eager to please the doctor. All these aspects tend to contribute to the myth that treatment with drugs is a prerequisite for regaining health.

Controlled trials in individual patients (n of 1 trials) have a long tradition in behavioural medicine¹ and have recently attracted attention in clinical medicine.^{2,3} Such trials may improve the certainty of a treatment decision in an individual patient, and a series of such trials may permit more general inferences to be drawn about a treatment.

Method of study

The main principle in the n of 1 trial is that the patient serves as his or her own control in a study of the efficacy of a new drug compared with placebo or another drug. The treatments are administered to the patient in a double blind, randomised, multiple crossover sequence (fig 1). Each treatment period is randomly assigned and the trial design is tailored to the clinical condition, the properties of the drug(s), and the statistical requirements. Separate measures of response are obtained for each treatment period, forming the basis for the evaluation of effect.

If similar prerequisites are applied for series of n of 1 trials as for a conventional group trial—strict entry criteria, uniform treatment procedures, consensus scales for outcome measures, and acceptable statistical tests—individual responders may be identified, common characteristics detected, and conclusions generalised to the target population.^{4,5}

Experiences in clinical medicine

Non-ulcer dyspepsia is a heterogeneous disorder in which patients are unlikely to benefit uniformly from one type of treatment. H₂ receptor antagonists are often prescribed for this condition, although con-

ventional clinical trials show conflicting results.⁶ In an attempt to identify individual responders to H₂ receptor antagonists in non-ulcer dyspepsia I and my colleagues devised a multicrossover model in which the effect of cimetidine was compared with that of placebo. We used treatment periods of one, two, and four days. The crossover model was later revised to improve its validity,^{7,8} and the current version requires that six tablets of cimetidine (400 mg or 800 mg) and six tablets of placebo are given in a double blind, randomised order. To adjust for instability in dyspepsia and to avoid possible carryover effects, the tablets are taken only when needed for relief of symptoms. The patient measures the alleviating effect of each tablet and an individual p value or confidence interval is determined. This method showed a beneficial effect of cimetidine among individual patients with reflux-like non-ulcer dyspepsia and confirmed the drug's effect on the symptoms of oesophagitis and peptic ulcer disease.⁹

In two earlier studies of the effect of cimetidine in non-ulcer dyspepsia we combined the results from many of n of 1 trials.^{7,8} A responder group was defined according to the individual p values obtained and compared with the non-responders in a multivariable analysis (fig 2). The results showed that the cimetidine responders had reflux-like or ulcer-like symptoms of dyspepsia.

Guyatt *et al* have run an n of 1 trial service since 1985, and in 50 of 57 completed n of 1 trials a definitive clinical or statistical answer was provided.⁹ In 15 trials the results prompted physicians to change their plan of management. Most trials were conducted in fibrositis and suspected obstructive airway disease. Case reports

FIG 1—Design and outcome of randomised controlled single subject trial comparing effect of cimetidine and placebo in non-ulcer dyspepsia. Treatments were randomised pairwise to ensure a confident spread. Bars represent response to separate treatment periods measured on categorical scale. Randomisation test for trial gave $p=0.02$

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FIG 2—Distribution of individual p values obtained in series of similarly conducted n of 1 trials

from other clinicians, however, show how a controlled single subject trial can be used to solve difficult therapeutic issues.^{10 11}

Doctor-patient relationship

The single subject trial incorporates the scientific method into the patient centred work and may reinforce the doctor-patient alliance. In symptomatic disorders the patient measures and evaluates his or her responses to the treatments, and the choice of treatment may evolve as a joint decision taken by the doctor and the patient. Thus more responsibility is given to the patient, who is also afforded new insight into the nature of his or her illness and the placebo effect. Improvement caused by a spontaneous recovery or a placebo effect is easier to show with such an approach, and this may make patients think more about the need for drug treatment.

Suitability of the single subject trial

Not all clinical entities or drugs are appropriate for n of 1 trials.^{2 3} Reversibility of the clinical condition is mandatory to allow for repeated treatment periods and comparisons. Stable conditions are less likely to produce errors, but unstable disorders could be studied if the treatment periods were extended to ensure that exacerbations were captured or the treatment was administered only when symptoms occurred.²

The drugs used in multicrossover n of 1 trials must be easy to present to the patient blind. As both treatments are tested in one patient over a rather short time they must be similar in appearance, taste, smell, and consistency and without side effects. A prompt onset and offset of action is an advantage because it shortens each treatment period, allows more periods, and thereby comparisons, and reduces the length of the trial.²

Statistics in single subject trials

The statistical principles for n of 1 trials are analogous to those for group trials, but there are some important distinctions.¹² The experimental unit in a group trial is the randomly selected subject whereas the equivalent unit in a single subject trial is the randomly allocated treatment period. The number of treatment periods has to be restricted to limit the duration of the trial. The corresponding low "sample size" makes n of 1 trials apt to overlook a difference in response (type II error). It is, however, fair to compare this risk with the opposite risk of falsely claiming a beneficial effect of the treatment (type I error) when the trial and error approach is used. Under the null hypothesis of no treatment effect the probability of such a conclusion is

50% or even higher if the regression and placebo effect is considered.

The n of 1 trial violates the assumptions that parametric statistical tests depend on. Accordingly, randomisation tests are recommended,¹³ although in clinical practice less sophisticated assessments may suffice.

When should n of 1 trials be performed?

Because an n of 1 trial is more laborious than the uncontrolled trial and error approach, the extra effort spent is justified only in chronic conditions that interfere with the patient's quality of life. Furthermore, there is no reason to conduct a controlled trial when convinced about the beneficial effect of a drug. Thus the clinical relevance of the n of 1 trial is restricted to conditions for which the efficacy of a drug intended to be used in long term management is uncertain. Today's trial and error approach, with its high risk of a type I error, probably results in an overconsumption of drugs. The main role in clinical practice of controlled trials in single subjects would probably be to cancel useless treatment rather than to advocate drug treatment. Clinicians could design and conduct such trials themselves if detailed guidelines were given² and placebo or an alternative control treatment were made available. Similarly, ready made test packages including placebo drugs could be manufactured and sold. This demands, however, the development of a new culture and expertise.

In research n of 1 trials are particularly attractive in the study of vaguely defined or heterogeneous conditions such as non-ulcer dyspepsia, fibrositis, irritable bowel syndrome, migraine, and obstructive pulmonary disease. In these conditions n of 1 studies may give new insight and generate hypotheses that may optimise the design of subsequent conventional group trials. Particularly in the early phases of new drug development the n of 1 trial could be used instead of the uncontrolled and open trials often used to determine a probable effect of a new drug, reveal serious side effects, identify optimal treatment regimens, and characterise the target population wherein a new treatment is likely to have a beneficial effect.¹³

In conclusion, the single subject trial bridges the gap between research and clinical practice. It may provide new insight into vaguely defined conditions, improve therapeutic decisions, strengthen the doctor-patient relationship, and create a more critical attitude towards drug treatment both among patients and doctors.

- Barlow DH, Hersen M. *Single case experimental designs: strategies for studying behavior change*. 2nd ed. New York: Pergamon, 1984.
- Guyatt G, Sackett D, Adachi J, et al. A clinician's guide for conducting randomized trials in individual patients. *Can Med Assoc J* 1988;139: 497-503.
- Johannessen T, Petersen H, Kristensen P, Fosstvedt D. The controlled single subject trial. *Scand J Prim Health Care* 1991;9:17-21.
- Spiegelhalter DJ. Statistical issues in studies of individual response. *Scand J Gastroenterol* 1988;suppl 147:40-5.
- Johannessen T, Fosstvedt D, Petersen H. Combined single subject trials. *Scand J Prim Health Care* 1991;9:23-7.
- Colin-Jones DG. Management of dyspepsia: report of a working-party. *Lancet* 1988;i:576-9.
- Johannessen T, Fjøsne U, Kleveland PM, et al. Cimetidine responders in non-ulcer dyspepsia. *Scand J Gastroenterol* 1988;23:327-36.
- Johannessen T, Kristensen P, Petersen H, et al. The symptomatic effect of one-day treatment periods with cimetidine in dyspepsia. *Scand J Gastroenterol* (in press).
- Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness. *Ann Intern Med* 1990;112:293-9.
- McLeod RS, Taylor DW, Cohen Z, et al. Single-patient randomised clinical trial: use in determining optimum treatment for patient with inflammation of Kock continent ileostomy reservoir. *Lancet* 1986;i:726-8.
- Petti TA, Unis A. Imipramine treatment of borderline children: case reports with a controlled study. *Am J Psychiatry* 1981;4:515-8.
- Edgington ES. Statistics and single-case analysis. *Progress in Behaviour Modification* 1984;16:83-119.
- Guyatt GH, Heyting A, Jaeschke R, Keller J, Adachi JD, Roberts RS. N of 1 randomized trials for investigating new drugs. *Controlled Clin Trials* 1990;11:88-100.

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