Statistics in Question

SHEILA M GORE

ASSESSING CLINICAL TRIALS— DOUBLE-BLIND TRIALS

The masking of observer and patient so that neither can identify the assigned treatment is the ideal way of avoiding subtly biased measurement (by the observer) or reporting (by the patient) of treatment outcome. Occasionally, response to treatment is unequivocal (death versus survival) so that double-blind comparison of treatments is a nicety of design rather than essential. More often treatments—for example, traction for low back pain—are such that double-blind comparison is practically impossible, though ingenious and valiant attempts have been made to cloak the assignments. Investigators are advised to describe how masking has been achieved or to explain clearly why comparison of masked treatments is not feasible.

(29) *What is meant by saying that a clinical trial is (i) double-blind; (ii) single-blind?*

(i) neither the assessor nor the patient can identify the assigned treatment

(ii) the assessor does not know the assigned treatment

COMMENT

(i) A clinical trial is double-blind (or double-masked) when neither the assessor nor the patient can identify the assigned treatment. In the Medical Research Council multicentre trial of glucagon and aprotinin in acute pancreatitis¹ patients were randomised in the ratio 1:1:2 to the three treatments: active

aprotinin and glucagon placebo; active glucagon and aprotinin placebo; glucagon placebo and aprotinin placebo. The matched placebos were supplied by pharmaceutical companies and all patients appeared to receive both drugs.

(ii) If the identity of the treatment is concealed only from the assessor then the trial is single-masked or single-blind. A comparison of cytotoxic drugs can seldom be double-masked because treatments, distinguished by their side effects or schedule of dosage, are apparent to both patient and doctor. White blood cell count and the results of a biopsy may nevertheless be reported unbiasedly because it is usually possible to ensure that neither the haematologist nor the pathologist is informed about the patient's treatment. The term "single-blind" has also been applied to trials in which only the patient is in the dark, although this is not nearly so important as the assessor being in the dark.

(30) *When is it important that a clinical trial is single or double-blind?*

—when knowing the assigned treatment risks bias on the part of the assessor (observing) or the patient (reporting/experiencing response)

—when response is measured and is not objective

COMMENT

When knowledge of the patient's treatment might introduce bias to the doctor's assessment of the response to treatment the trial should be at least single-blind. If, moreover, the patient's response to the treatment or his reporting of that response might be prejudiced by knowing which treatment he receives the clinical trial should be double-blind or double-masked.

Bias in the recording of date of death is unusual. Systematic error in the reporting of time to the development of metastasis is possible, however, if one treatment group is unwittingly followed up more regularly than the others or if the methods used to detect metastases vary between treatment groups.

Prejudging a particular treatment may lead to unconsciously biased reporting of the clinical history, blood pressure, cell counts, radiographic films, biochemical test results, and many other measurements. A professor of my acquaintance has said that his assistants are keener on his ideas than he is himself.

Anticipation: "a positive result will please the boss"

Anticipation—"a positive result will delight the boss"—is one of the 13 mortal sins of clinical assessment.²

The Northwick Park trial of electroconvulsive treatment (ECT)³ is an interesting example of double-blind comparison between real and simulated ECT. The treatment allocation was known only to the psychiatrist who administered the ECT and to the anaesthetist. Neither of these doctors helped to care for or assess the patients; moreover, the patients, who completed scales for the self-assessment of anxiety and depression, did not know to which treatment group they belonged. The preconceived notions that the patients may have had about the effectiveness of electroconvulsive treatment could therefore hardly bias their response.

(31) *What tell-tale signs can unmask treatments?*

—smell, taste, shape, colour

—frequency (bd or tid)

—conversation between doctor and patient

—side effects

COMMENT

The tell-tale signs⁴⁻⁵ that can unmask treatments include their smell, taste, or texture. Phillips and co-workers⁶ compared atenolol versus adrenaline eye drops and the two combined in the treatment of glaucoma. Although eye discomfort was negligible, an unusual taste distinguished the "active" drops from the saline drops. The authors were careful not to claim that the trial was double-masked. In the South Wales dextran trial⁷ one anaesthetist was suspected of attempting to differentiate between the dextran and placebo solutions by shaking them.

Other clues are the shape or colour either of the drugs themselves or of their containers. Frequency of administration—for example, bd versus tid—or toxicity is sometimes sufficient to distinguish treatments. Moreover, in single-blind trials the patient may simply tell the radiographer, tonometrist, or registrar which treatment has been given.

Anderson *et al*⁵ have questioned the rather loose way in which the term "double-blind" is often used in the reports of clinical trials, suggesting that authors state what steps were taken to ensure that the preparations were indistinguishable, and, moreover, test the effectiveness of these measures. In a double-blind trial to test whether beta-blockade affected surgical performance⁸ seven surgeons each took a 40 mg tablet of oxprenolol or placebo one hour before four operating sessions. The order of tablets had been randomised so that each surgeon took a 40 mg tablet of oxprenolol before two sessions and a matched placebo tablet before the other two sessions. After completing each operating list the surgeons were asked: "Did you take a beta-blocker?" Out of 28 responses the surgeons were wrong 17 times and correct 11 times and so were surprisingly unaware of whether they had taken oxprenolol or placebo.

Of course, blind comparison of treatments is not always possible. In a trial that compared the wound infection rate after abdominal operation⁹ patients were randomly allocated to (a) an untreated control group, (b) a group receiving preoperative lincomycin and tobramycin, or (c) a group that received a local infusion of povidone-iodine. A survey of clinical trials published in the *Lancet* from July to December 1977 indicated that about half the trials that could have been double-blind were so. Investigators may have been reluctant to explain why masking was not feasible. Such explanation should be encouraged and ridiculous comments avoided—such as, "Patients were instructed to swallow the tablets without tasting them as taste could have interfered with the double-blind nature of the trial."

Side effects

(32) *Guttae atenolol and guttae adrenaline are compared in a double-blind randomised cross-over trial. Elderly patients with glaucoma attend hospital for all-day tonometry on two study days. The contents of the bottle labelled "Patient 3, Day 1" have evaporated. Patient 3 is waiting. What should the tonometrist do?*

—use the assignment for patient 3, day 2

COMMENT

The tonometrist solved the problem neatly. She rejected the first five solutions for the reasons shown and settled for the sixth.

Solution 1 Send the patient home—was rejected because a return visit would impose an unnecessary burden on an elderly patient. Moreover, the trial design assumed that groups of four patients would attend together.

Double-masked randomised controlled trial in ophthalmology

Problem: the contents of the bottle labelled "Patient 3, Day 1" have evaporated

Solution: ?

Solution 2 Use the assignment for "patient 4, day 1"—was unacceptable because that patient had also come to hospital.

Solution 3 Withdraw patient 3—was rejected because reduction in patient numbers should be avoided and patient 3 would have made a wasted journey.

Solution 4 Replace the contents of the bottle—was impossible because the tonometrist did not know what the contents had been.

Solution 5 Statistician breaks the randomisation code to enable the pharmacy to replace the eye-drops—seems to be acceptable provided that the treatment code is not revealed to the tonometrist. But a further constraint is that ocular tension shows diurnal variation and a strict time schedule was imposed on the study. Unless the replacement could be made quickly this solution would also be inadequate.

Solution 6 Use the assignment for “patient 3, day 2”—was adopted. The patient was neither sent away nor kept waiting; the time schedule for the trial was adhered to; the tonometrist and the patient remained masked. The statistician was contacted before the patient's second visit and replacement drops obtained from the pharmacy. The balance of the trial design was slightly perturbed but that was the statistician's problem.

The example is included as a reminder that the double-blind nature of a clinical trial may make for unusual experimental difficulties. It is important to have an arrangement whereby the treatment code may be broken if a patient is withdrawn from the trial and subsequent care depends upon which trial treatment the patient was assigned to. It is often possible to specify an emergency treatment that may be used on any patient in need without breaking the code; and this should be arranged, if possible. In a long-term clinical study, if it is important that treatment allocation is not revealed to the trial doctors, a peer review group should be appointed with whom the statistician can discuss interim results and who will adjudicate for their colleagues on ethical issues. Only analyses of the trial as a whole (without

reference to individual treatments) are presented to the participants in the trial.

References

- 1 MRC Multi-centre Trial of Glucagon and Aprotinin. Death from acute pancreatitis. *Lancet* 1977;ii:632-5.
- 2 Hart FD, Huskisson EW. Measurement in rheumatoid arthritis. *Lancet* 1972;ii:28-30.
- 3 Johnstone EC, Deakin JFW, Lawler P, *et al.* The Northwick Park electro-convulsive therapy trial. *Lancet* 1980;ii:1317-20.
- 4 Hill LE, Nunn AJ, Fox W. Matching quality of agents employed in “double-blind” controlled clinical trials. *Lancet* 1976;ii:352-6.
- 5 Anderson TW, Ashley MJ, Clarke EA. Not so double-blind? *Br Med J* 1976;ii:457-8.
- 6 Phillips CI, Gore SM, Gunn PM. Atenolol versus adrenaline eye drops and an evaluation of these two combined. *Br J Ophthalmol* 1978;62:296-301.
- 7 Davies TW. Dextran or heparin? *Lancet* 1978;ii:1315-6.
- 8 Foster GE, Makin C, Evans DF, Hardcastle JW. Does β -blockade affect surgical performance? A double blind trial of oxprenolol. *Br J Surg* 1980;67:609-12.
- 9 Galland RB, Saunders JH, Mosley JG, Darrell JH. Prevention of wound infection in abdominal operations by preoperative antibiotics or povidone-iodine. *Lancet* 1977;ii:1043-5.

Sheila M Gore, MA, is a statistician in the MRC Biostatistics Unit, Medical Research Council Centre, Hills Road, Cambridge CB2 2QH.

No reprints will be available from the author.

MATERIA NON MEDICA

Vienna

The visitor to Vienna with an interest in medical history will remember Osler's respect for the great figures in its medical school. The gynaecologist will remember not only Gerhard von Swieten and his famous advice, which must have contributed to Maria Theresa's becoming a 16 para, but also Semmelweis and Wertheim. The dermatologist will think of von Hebra, the chest physician of Auenbrugger and Skoda, the pathologist of Rokitansky. The surgeon honours the name of Billroth. Meynert, Mesmer, Gall, Krafft-Ebing, Wagner-Jauregg, and Freud interest the neurologist and the psychiatrist. The medical philatelist knows that Austria honoured these men on her stamps and may search in some of the many stamp shops.

Linie D runs from Sudbahnhof to Nussdorf. The psychiatric pilgrim can board the tram at Babenberg Strasse outside the Kunsthistorisches Museum, where he may have seen the Holbein portrait of Dr John Chambre (or Chambers), Henry VIII's physician. It passes the university, where the busts of the great men are on view in the courtyard and he alights at the Berggasse. When he opens the door of No 19 he is confronted by a notice which says that the Sigmund Freud Museum is on the first floor. It is necessary to ring the bell for admission. For 20 schillings he has the loan of a very informative guide book to the shrine established in the apartment which Freud occupied from 1891 to 1938. The entrance hall is as it was in Freud's time. Here are gathered relics of the great man: his hat, his stick, his valise. A few of his collection of antiquities, some of his furniture, and some of his books are on display. This is remarkable when one remembers that his collection of antiquities was dispersed, his furniture sold or sent to England, and his library disposed of. In the first room are his couch and certificates of his election to learned societies. There are photographs of his parents, the early psychoanalytic congresses, and portraits of his early disciples. Photocopies of documents range from his birth certificate to the Nazi decree dissolving the Vienna Psychoanalytic Society, successor to the Wednesday Evening Society which met in his waiting room on the lower floor. Reprints of his published works remind us of the wide span of his accomplishments from the early neurological studies to “Moses and Monotheism.” Particularly pleasing is the photograph of the presentation of the parchment of the Honorary Fellowship of the Royal Society of Medicine after he had arrived in England in 1938.

Visitors move round reverently, talking in hushed tones. Little smiles of satisfaction appear when something familiar in the psycho-

analytic canon is recognised. In the library they can buy copies of books in English and German: the Ernest Jones biography is prominent. Also on sale are postcards and photographs and copies of the catalogue.

This unbeliever left the Museum marvelling at the devotion and industry which his followers have shown in raising this impressive memorial to their Master.—W L JONES (consultant psychiatrist, Mapperley, Nottingham).

R after L?

Do you know anything quite so terrifying as sitting beside your daughter (maybe your son also but I have not yet had that experience) when she is practising her driving on *your* car? But at least we then had L plates fore and aft so that most drivers did allow some latitude and showed a little good-humoured patience.

We have, however, just been for our test. I wonder if all the test centre waitingrooms are quite as forbidding as ours with notices on the wall in big black type warning: “A man who offered a bribe to an examiner has been fined £200 by a Magistrates' Court”; and again, “A man who impersonated a learner driver in the test was sentenced at a Crown Court to 3 months imprisonment suspended for 2 years. The man on whose behalf he had taken the test was sentenced to 12 months imprisonment.” About half an hour later there were sounds of exultation from without—she had passed. She returned home radiant but my wife reports that I looked pale and shaken. I have been out with her since and have noticed a slight diminution in concentration and, of course, she is now given no leeway by other drivers. Clearly she will need, like all other drivers who have just passed their test, another 12 months' experience to include motorway and night driving.

I wonder why we have not adopted universally the restricted licence scheme in force in Northern Ireland? This means that for 12 months after passing the test new drivers have R plates and are not allowed to drive at speeds over 45 mph on any roads including motorways. After this they get a full licence. Ideally they should have to pass another test before getting the full licence but this is probably not feasible with the present shortage of examiners. But at least the adoption of the limited R scheme would be an additional contribution to road safety at minimal cost.—MYER GOLDMAN (consultant radiologist, Liverpool).