Statistics in Question

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ASSESSING CLINICAL TRIALS—DESIGN I

Treatments may be compared between groups of patients, within-patient simultaneously, or by patients crossing over from one treatment to another. To assess the synergism of propranolol and tienilic acid for the treatment of moderate essential hypertension,¹ for example, it was necessary to study a factorial structure of four treatments: placebo, propranolol, tienilic acid, and tienilic acid combined with propranolol. In a single experiment it is often possible and efficient to investigate the effects and interactions of two or more, perhaps unrelated, treatments by assigning patients to all treatment combinations. Such designs—factorial—should be considered more often.²

(7) What is the advantage of within-patient comparison of treatments?

—usually far fewer patients are needed

—it can be applied when looking for short-term symptomatic relief of a chronic condition

—disadvantage: beware systemic action and contamination between treatment areas

COMMENT

The advantage of within-patient comparison of treatments is that usually far fewer cases are needed than in a design that calls for patients to be randomised to receive one treatment or another. The reduction in the number of patients comes about

without loss of power whenever the responses by an individual in matched sites—for example, right and left eye, right and left scalp—are not as variable as the responses compared between individuals. This is what usually happens in medicine.

Within-patient comparison of treatments should be avoided, however, when treatments can act systemically or when there is the possibility of contamination between treatment areas because bias, unbidden and of unknown extent, intrudes.

Four studies of the induction of hair growth by dinitrochlorobenzene (DNCB) in patients with alopecia areata were reported in the same medical journal.³⁻⁶ All four used within-patient comparison of DNCB versus no treatment. Readers noted^{5, 7, 8} that DNCB might act systemically in addition to having a local effect; moreover, itching or rubbing the scalp might have contaminated the untreated area. The claims made for DNCB were, if anything, conservative, and DNCB needs to be compared with other treatments and with spontaneous remission. Such a trial would entail randomising patients to one treatment or another.⁶

Within-patient comparison

Alopecia areata³: treated side should be chosen at random for each patient

Note: by itching or rubbing patient may contaminate the untreated area

(8) What is an example of treatments that must be compared between groups of patients?

—simple versus radical mastectomy for unilateral breast cancer

COMMENT

The nature of certain treatments precludes within-patient comparison. Simple versus radical mastectomy for stage 1 or 2 unilateral breast cancer can obviously only be compared between groups of patients randomised to one treatment or the other. Simple design principles suffice for many clinical studies. Out of 38 clinical trials reported in the *Lancet* over six months, 28 compared treatments between groups of patients. Mostly two treatments were compared (25 studies). No trial used a factorial design.

(9) What can seriously complicate the analysis of cross-over designs?

—order effects

—treatment carry-over

COMMENT

An interesting example of a cross-over design was the experiment on how oxprenolol affected stage-fright in musicians.¹⁰

Twenty-four string players each gave two solo performances before an invited audience in the Wigmore Hall. Order effects (systematic changes between first and subsequent assessments) are not unusual in cross-over trials, and they complicated this example because second performances were rated higher than first performances. An even more serious complication in analysing cross-over designs is when the effect of an earlier treatment persists during one or more subsequent treatments—that is, there is treatment carry-over. Treatment carry-over should be avoided either by inserting a “wash-out period” between treatments or by adopting a different design altogether.

Hills and Armitage¹¹ wrote an excellent review on the design and analysis of cross-over trials describing how to use pretreatment or base-line observations, how to look for order effects and evidence of treatment carry-over, and how to recognise unbiased treatment comparisons. This paper is essential reading for anyone who is planning a cross-over trial.¹² I suggest, in addition, that doctors consult a statistician about cross-over experiments.

References

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I was exposed to mumps during two epidemics at school without being infected. Aged 50 I developed non-parotitic mumps, characterised by encephalitis and orchitis, fortunately with no sequelae. Is mumps usually more severe in adults than in children? My son aged 20 has not had mumps. Should he be vaccinated?

Mumps is a less infectious disease than either measles or rubella,¹ and it is therefore quite possible to reach adult life without being infected, although subclinical infection is common. There is considerable evidence that mumps and its complications may be more severe in adults than in children. For instance, in the United States from 1966 to 1975 some 40% of deaths from mumps occurred in patients over 40, and the age distribution of mumps encephalitis showed a larger proportion of cases among older people.² In Alaska mumps orchitis occurred most often in those aged 15-29.¹ The absence of a definite history of mumps by the age of 20 does not necessarily mean lack of immunity: of 124 young adults who said that they had not had mumps, 87% were found to have antibody.³ Nevertheless, for peace of mind and to avoid the risk of catching mumps from children or eventual grandchildren, it would be well worth investigating the antibody state of any man of 20 with no history of mumps. Immunity can be checked quickly and cheaply by radial haemolysis, and a negative result should be followed by vaccination.

¹ Reed D, Brown G, Merrick R, Sever J, Feltz E. A mumps epidemic on St George Island, Alaska. *JAMA* 1967;199:967-71.

² Hayden GF, Preblud SR, Orenstein WA, Conrad JL. Current status of mumps vaccine in the United States. *Pediatrics* 1978;62:965-9.

³ Mortimer PP. Mumps prophylaxis in the light of a new test for antibody. *Br Med J* 1978;ii:1523-4.

What apparatus is available for achieving electroejaculation in either paraplegic or impotent patients who wish to impregnate their wives?

Although electroejaculation has been used by veterinarians for many years, only a few centres have applied the technique to man. Each centre has developed its own apparatus¹⁻³—usually a form of rectal probe delivering a small electric current to the pelvic nerves. An electrode mounted on a glove-finger¹ may be purchased from Mr C M Andrew, 43 Landcroft Road, London SE22. In a series¹ of 84 paraplegic men on whom this apparatus was used semen was obtained from 50, although 14 of these had only retrograde ejaculation, and few men produced good semen. Multiple attempts may be needed. Some wives have been taught to use this apparatus on their paraplegic husbands at home. The semen may be used for artificial insemination (erection is usually only slight), but only one pregnancy has been achieved with this apparatus, and very few pregnancies have been achieved in other centres.^{2,3} If the spinal cord lesion is above T12 stimulation is pain free, but in men with lower lesions it may produce severe pain. The apparatus has been used in non-paraplegic men with ejaculatory failure, and in these cases general anaesthesia is required. Peripheral nerve function is necessary for electroejaculation, which is therefore probably unsuitable for men impotent because of peripheral neuropathy.

¹ Brindley GS. Electroejaculation: its technique, neurological implications, and uses. *J Neurol Neurosurg Psychiatry* 1981;44:9-18.

² Francois N, Maury M, Jouannet D, David G, Vacant J. Electroejaculation of a complete paraplegic followed by pregnancy. *Paraplegia* 1978;16:248-51.

³ Thomas RJS, McLeish G, McDonald IA. Electroejaculation of the paraplegic male followed by pregnancy. *Med J Aust* 1975;ii:798-9.