PRACTICE OBSERVED

Research in General Practice

Clinical trial in general practice?

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Why I started

Any doctor worth his or her salt should be asking questions about the fascinating array of problems about which we are consulted every day. The finest aspect of general practice is its colourful diversity, and yet even this has been seen as a disadvantage by those who think that only specialist clinics see enough material of a unified nature to permit research. There are many areas of the generalist's work that are highly suited to research: one of these is acute respiratory tract infections, which form about 60% of the work load of doctors working in primary health care.

So common and mild are many respiratory infections that often they are not even regarded as diseases; furthermore, there is no clear relation between many of the syndromes and the organism concerned,[1] and host resistance is equally variable. Dietary, socioeconomic, hereditary, family, and atmospheric factors all modify the individual's experience of respiratory symptoms and diseases. Doctors also show very diverse habits in diagnosing the individual syndromes,[2] and antibiotics are often overprescribed, to the detriment of the environment, the patient's expectations, and the person who foots the bill.

Clear guidelines for treatment are difficult to formulate because of this lack of insight into the environment-host-organism interrelation, and the field has been left wide open for exploitation by advertising, fashion, and dogmatic educators. The double-blind randomised controlled trial is probably the best way to begin to provide some of the answers to such awkward questions because it is possible to control for many factors, known and unknown, while testing a particular hypothesis or question.

The question I will use to illustrate the use of the randomised controlled trial is: Do patients with cough and purulent sputum merit antibiotic treatment?[3]

When I first posed this question in 1972 it seemed clear that patients with cough and purulent sputum were not treated uniformly by doctors. Some were given broad spectrum antibiotics, some were given penicillin, some were given cough mixtures, and some were given advice about soothing home remedies. A few were even sent off with a flea-in-the-ear about this being a "non-illness" that should be ignored. The scene was set for a trial to establish whether or not treatment with antibiotics would influence the symptoms or signs of this problem, which some patients clearly regard as an illness and some doctors are prepared to label as a disease. A controlled trial would also provide valuable information about the natural history of the problem.

What I did

Several stages were followed to get the trial underway: (*i*) search of literature; (*ii*) informal survey of local doctors' opinions; (*iii*) writing of a protocol; (*iv*) ethical committee approval; (*v*) application for research funds and support; (*vi*) discussion with statistical adviser; (*vii*) staff appointments; (*viii*) involvement of research practices; (*ix*) start quality control. In this article I cannot deal with each aspect fully, but several points are worth making because they are often overlooked and cause annoyance or regret.

(*i*) A literature search for related work is vital before a protocol is written because it is sad to work on a project only to find that someone else has done it already or that one of the methods used was less than ideal. Medical librarians, secretaries of local postgraduate centres, and the librarian of the Royal College of General Practitioners are all extremely helpful if you are in

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doubt about where to begin. It is also wise to read reviews of your subject written during the past five years or so to see whether your ideas are innovative or complementary to existing trends.

(*ii*) Consultations with local doctors and researchers for opinions can be helpful for both practical and political reasons. I found that the doctors were divided into those who treated cough and purulent sputum with antibiotics and those who did not. They were also helpful in clarifying suitable diagnostic criteria and exclusions from the study. For example:

Included: All patients from three group practices aged over 14 years who had cough and purulent sputum for up to seven days.

Excluded: Those with abnormal clinical signs in the chest on auscultation. Those with persistent sputum expectoration in winter months. Those with other chronic disease (diabetes, emphysema, etc). Those sensitive to tetracycline. Those pregnant (or possibly pregnant).

The aim was to study a healthy adult population with cough and purulent sputum of recent onset (=middle respiratory infection). This is not the most common of respiratory infections, but it was the most controversial because it was neither a true lower respiratory infection with chest signs (in which there is a high probability that the patient will be given an antibiotic) nor an uncomplicated upper respiratory infection (in which there is a high probability that the patient will not be given an antibiotic). I estimated that 200 cases would take about a year to collect from a population of 8000 patients . . . but I proved to be wrong (see below).

(*iii*) Writing a protocol is an excellent discipline, even if research funds are not needed, because it requires a review of the literature and a description of the question to be tested, the methods to be used, the resources likely to be needed, how analysis of results is to be done, and the likely implications for

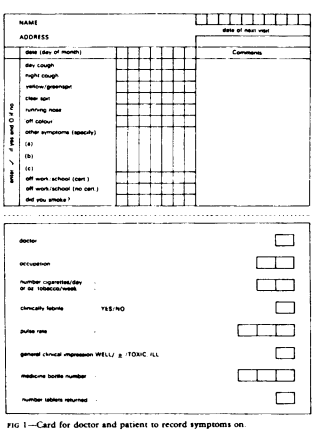

FIG 1—Card for doctor and patient to record symptoms on.

the future. I had decided to try to answer two basic questions: (*a*) Does antibiotic treatment modify the clinical course of middle respiratory infection in otherwise healthy adults who have been unwell for up to a week? (*b*) Does such treatment influence the incidence of subsequent infections?

These questions meant that I had to design a card for the doctor to record clinical symptoms and signs and a card for the patient to self-record symptoms while taking treatment or placebo on a day-to-day basis (fig 1). The doctors had to agree to review the patients at the end of week 1 and stop treatment if both doctor and patient were satisfied with the outcome, and if sputum was clear. Question (b) refers to the incidence of infections brought to the doctor and implies a need for either patient self-recording for a further six months (which is impractical) or using practices that keep good medical records to ensure that all day and night consultations and visits were recorded.

(*iv*) Ethical committee approval: a brief account of the study (one page of typescript) is usually sufficient, and the secretary of the local medical committee will ensure that it is processed by the next meeting.

(*v*) A clinical trial often involves drug treatment, and pharmaceutical companies are very helpful. Pfizer Limited were kind enough to supply doxycycline capsules and identical placebo capsules in randomised, numbered bottles. The randomisation code was supplied in a sealed envelope and held by the statistical adviser until the project was completed. This meant that a DOUBLE-BLIND format was achieved with neither doctor nor patient knowing who was receiving the active drug.

The Welsh Medical Research Committee supported a part-time health visitor to assist with fieldwork and quality control. Every area has local research committees that supply small grants, but consultation with local academics will always help in the search for an appropriate fund-raising body if the researcher is in doubt.

(*vi*) A statistical adviser who is concerned from the outset is an asset and a friend, saves no end of time, and will do all the analysis of data, which few clinicians have the inclination or the skills to perform. If he does undertake more than advice do consider including him as a co-author—it is courteous and builds happier relationships for later projects.

(*vii*) Staff appointments are often necessary in clinical trials because clerical and fieldwork can be tedious or impossible if the clinician is trying to do it in his "spare time." I worked through the personnel and finance offices of the medical school, but practice managers are also helpful and many research or academic institutions will act as an "umbrella" for the general practice researcher and provide help with such matters. See the departmental head and you can expect a warm reception if you have done your homework and know what you hope to do.

(*viii*) Quality control of data is a recurrent nightmare for research workers: the thought that all your efforts may be smashed by discovering that observers are inconsistent or biased or that you have omitted a vital check which invalidates your results. Have no fear; no research is perfect, but you must try to establish quality checks. In the study on middle respiratory tract infection the following checks were made:

(*a*) All 22 doctors who participated were briefed by the researcher and subjected to a blind clinical signs study in which a series of patients seen by the doctors in their own surgeries were also auscultated by an independent clinician. Both doctors recorded the objective signs independently. This was repeated until the researcher was satisfied that chest signs were being interpreted consistently.

(*b*) Patient compliance when recording symptoms and taking treatment was assessed by counting the capsules in bottles returned by patients at the end of treatment and by a health visitor calling at the homes of a one-in-five sample of patients during the first week of treatment to check on recording and capsule count. The patients were not told that the health visitor would be calling.

(*c*) Respiratory diagnoses were checked daily on doctors'

records to identify those who qualified for the trial but were not entered into it: 12 were found. Of these, the doctor forgot in seven, one could not swallow capsules, one had been nauseated by doxycycline previously, and three had refused to participate. (Two others started the trial but were non-responders because one changed his mind and the other could not be traced.)

Quality control was a time-consuming but essential part of the study, and I would have failed to find the time for this task without the assistance of a nurse or health visitor field-worker. She also played a valuable liaison role between the 22 practitioners and ensured that the capsule dispensers were always full and a good supply of cards was available in every practice. Reminders to doctors to include all suitable cases were sent at regular intervals but the field-worker's presence in the practices was probably more important.

What I found

The first discovery was that I could not complete the study in one year as my estimates about the frequency of middle respiratory tract infection had been optimistic. This is a very common error in clinical trials and hard to avoid because one is never 100% sure about the incidence of anything until a full survey is completed. Opinions are notoriously unreliable, and even a pilot study can lead to gross miscalculation.

The most important finding is illustrated in fig 2. Doxycycline

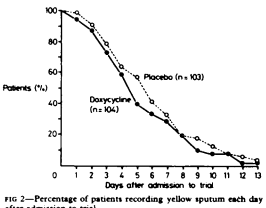

FIG 2—Percentage of patients recording yellow sputum each day after admission to trial.

and placebo groups were no different, whether judged by symptoms or duration of illness, purulent sputum, or time off school or work. The figure also illustrates the natural history of middle respiratory tract infection, nearly 30% of patients still having purulent sputum at seven days but this resolved over the next seven days. Similar trends were seen for other symptoms (cough, malaise, fever, headache, etc).

Could the results be biased? Yes, all results can be biased, even those from double-blind randomised controlled trials if the randomisation process fails to provide two identical groups for study. This can happen by chance, and it is another nightmare for the researcher when he or she analyses the results. Fortunately, this study did not suffer from this chance defect but we had to show that the groups were balanced by age, sex, symptoms on entry, duration of illness, severity of illness, compliance with drug taking, occupation, and smoking habits.

SIDE EFFECTS OF TREATMENT

All treatments have some possible side effects, and a drug that causes rashes or nausea or diarrhoea is much less likely to be taken by patients than one that has no side effects. In a trial this can be a cause of failure and can lead to drop-outs from half of the study unless all patients are warned about possible transient or minor symptoms. In this study equal numbers of patients on placebo and doxycycline felt nauseated, and so it is likely that this was an effect of the infection or expectations which were set by the clinicians. None of the subjects, however, actually stopped taking the drug for this reason.

The lessons I learnt

(1) Always allow 50% additional time on your estimate for project duration.

(2) Plan for adequate fieldwork or clinical assistance, or both, even if you think that your present staff can carry the additional load.

(3) Take advice from as many sources as possible before starting the project. This helps to avoid mistakes and miscalculations, but it is time-consuming.

(4) The randomised controlled trial is a very powerful research tool that yields useful results, but it is also very demanding of time and resources. Sometimes small differences between two groups cannot be shown until very large numbers of cases are recruited into the trial. A statistician must guide you or you will be tempted to take short-cuts that you will regret subsequently.

The conclusions I was able to draw

Six years after the project on middle respiratory tract infection was published I find myself identifying two sets of conclusions. The first is a constant: that otherwise healthy adults who present to their doctors with cough and purulent sputum of up to seven days' duration and whose chests show no abnormal signs on auscultation—that is, middle respiratory tract infection—usually get better as quickly without as with antibiotic treatment. This finding has also been corroborated by controlled trials in children with various respiratory infections and in adults given early treatment for colds and influenza-like illness.[4–6] This study[3] also provided useful information about the natural history of middle respiratory tract infection by confirming that it is usual for symptoms to persist for up to a week, and in a third of patients they persist for several days longer. Patients can now be told what to expect, and this is a very important part of management, which other work has also highlighted.[7]

A second set of conclusions relates to the way the results of the study have been used by doctors and researchers since publication: it has been disappointing to find that many clinicians continue to prescribe antibiotics for middle respiratory tract infection, and the study has been misquoted in defence of this strategy. It has also been misquoted in defence of not giving antibiotics to patients with chronic bronchitis with acute exacerbation. I can only conclude that some clinicians seek to justify their clinical behaviour by misuse of references. Perhaps if more clinicians conducted clinical trials themselves they would learn how cautiously one has to interpret original work and that one detailed study can only provide a further fragment for the patchwork quilt of knowledge that we call science.

Opportunities for similar research

Evidence for the limited efficacy of antibiotics in many respiratory tract infections is now well documented, but there is a paucity of controlled clinical research into the relative efficacy of substances that are supposed to provide symptomatic relief. Analgesics, decongestants, cough suppressants, expectorants, and soothing vapours are all used, but do they have

a pharmacological action or do they simply pander to mankind's tendency to seek magical cures for illness? A host of studies is waiting to be done in respiratory infections alone, but each one will need painstaking work on a large number of subjects to provide a definitive answer. In the meantime the Department of Health is becoming more hard-line in its attitude to paying for symptomatic treatment, so if you have a favourite mixture you had better evaluate it quickly!

If you do not like respiratory infections just try to examine the evidence for other favourite treatments. How is your management of: muscle sprains, low back-ache, tension symptoms, dysuria, tennis elbow, etc? General practice is riddled with remedies for symptoms or syndromes and many still await careful evaluation in the community. Most treatments will swing with fashion and advertising until a solid evaluation in the form of a clinical trial casts fresh light on the problem. Do not forget, however, that treatment other than drugs is also amenable to this approach and we need more assessments of non-drug treatments in general practice.[7] We also need to keep a watchful eye on those non-medical treatments that are being promoted and applied by healers on the fringes of medicine because some are harmful and others may merit our serious attention.[8]

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Organising a Practice

Communication in the practice

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Two changes in the pattern of British general practice over the past two decades have increased the need for good communications in practices: more and more doctors practise in partnerships and the number of employed and attached staff has grown. This is well illustrated in our semirural practice near Bristol. When I joined my late senior partner more than 25 years ago there were just the two of us and a part-time secretary. Her job was to sit in my partner's dining room answering the telephone and entering requests for visits in the appropriate book. Between calls she kept up to date with the latest issues of *Vogue*, *Country Life*, and *The Tatler* before they came to rest in the waiting room. Charming and decorative, she has long since retired to raise a family, and life has become more complex. Today there are seven partners, two trainees, a practice manager, and no fewer than 28 other non-domestic staff working in the practice, which now is run from a converted private house in the original village and from a health centre two miles away, where a small new-town for Bristol commuters has grown. Many of these people are part-time, of course, which increases the communication problem, and the treatment-room nurses at the health centre are shared with another practice.

When we moved into the health centre the county medical officer of health bet me that the practice would split in two within five years. I think it is a measure of our success in maintaining good communications that 10 years later we are still a closely knit practice and fully expect to remain so. No partner has ever left, and secretaries and nurses seem to do so only if their husbands move or they become pregnant, and even then they usually return soon after. One receptionist joined us 25 years ago to help out for a few weeks and has been with us ever since.

There are many practices that can claim the same degree of stability and staff loyalty. All will be different, but all would probably agree that good communications are high on the list of factors that have led to their success. How then is close liaison between six individualists of quite different personalities achieved, so that in the end coherent policies emerge, decisions are taken, everyone feels involved, and splits do not form within the group? Partners usually communicate informally during their day-to-day contact (all right if there are only two or three and all work from the same building) and more formally by practice meetings.

Practice meetings

There seems to be surprisingly little consensus among practices as to the form practice meetings should take and how often they should be held. We hold a lunch-time meeting on the same day each week and at the same time. This is attended by all partners, the two trainees, and the practice manager. A simple lunch is prepared on the premises and there is always a bottle of wine—vin ordinaire for routine meetings and something a little better when guests are present. Some practices hold evening meetings, but I would not recommend this as a routine. Stephen Taylor[1] advised either fortnightly or monthly—"between 8 and 9 pm in the drawing room of one of the partners"—but nowadays most of us value our time off too highly to want to turn out

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