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Therapeutic fashion and publication bias: the case of anti-arrhythmic drugs in heart attack

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Introduction

Disturbances of heart rhythm (arrhythmias) are common during and soon after heart attacks (myocardial infarctions), and these arrhythmias often precede and lead to early death. In the 1970s, it was found that the local anaesthetic drug lignocaine (lidocaine) suppressed arrhythmias, and it seemed obvious that giving anti-arrhythmic drugs would reduce the risk of early death after heart attack. The problem was that this obvious theory was wrong, but this was difficult to recognise from small clinical trials looking only at effects on arrhythmias, not outcomes that really matter, like deaths. Large clinical trials of anti-arrhythmic drugs done to assess their effects on mortality were not reported until the late 1980s, and these showed that the drugs actually increased mortality, probably because they can increase arrhythmias.[1,2] Apart from trials that were too small assessing outcomes that were of little importance to patients, how did therapeutic fashion and publication bias contribute to the delay in discovering the lethal effects of anti-arrhythmic drugs given to people experiencing heart attacks?

The effects of therapeutic fashions on research

Medicine follows fashions. Around 1980, a fashion in cardiology was to use beta-blocker drugs in people recovering from heart attacks. Although the first (poorly controlled) trial of one of these drugs (propranolol) after myocardial infarction had been published in 1965,[3] the results of several small controlled trials remained unconvincing until the early 1980s,[4] with publication of a Norwegian trial of timolol (Norwegian Multicentre Study Group, 1981).[19]

Like most people at the time, we did not appreciate the need for trials large enough to study adequate numbers of important outcomes, like death.[5] Indeed, the beta-blocker era contributed hugely to clinical trial development in cardiology. However, when we found that beta-blockers had little or no effect on arrhythmias after myocardial infarction,[6] we lost interest in these drugs and focused instead on a new anti-arrhythmic agent, lorcainide.

Lorcainide was a class 1C anti-arrhythmic agent which had been shown to be effective against experimentally induced arrhythmias in animals and some arrhythmias (ventricular extrasystoles) in patients.[7–9] In 1980, lorcainide had not previously been studied in patients with myocardial infarction. Fashion (based on inadequately tested theory) dictated that if a drug was to reduce mortality after myocardial infarction it had to be able to suppress what were then called 'warning' arrhythmias (ventricular tachycardia, frequent ventricular extrasystoles, couplets and triplets). Accordingly, we decided that a study of the effect of lorcainide on post-infarction arrhythmias had to be done before any study of the effect of the drug on mortality.

The hospital ethics committee approved our plans, and we thought that about 100 patients would be enough to show a 25% reduction in 'serious' arrhythmias. However, with a trial of this size we did not expect to detect an effect of the drug on mortality. Its effects on arrhythmia were our primary interest. Patients were excluded if they had an arrhythmia that needed treatment, if they were taking a beta-blocker, if they had heart failure, or if their blood pressure was low on admission to our coronary care unit. Within one hour of admission eligible patients were allocated at random to receive either lorcainide or placebo. Their electrocardiographs were recorded and analysed by people who were blinded to which of these a patient had received. In the absence of obvious unwanted events, treatment was continued for six weeks.

We found that, compared with placebo, lorcainide was associated with a statistically significantly lower frequency of 'serious' arrhythmias, but that it was also associated with a higher frequency of deaths. In the placebo group, only one patient of 47 died, whereas in the lorcainide group there had been

nine deaths among 48 patients. This difference did not worry us particularly: the overall death rate (10%) was about what we had expected, we had become used to the confusion caused by small trials with few outcomes, and we assumed that the excess deaths in the lorcainide group had probably occurred by chance because there did not seem to be any pattern in the causes of death. For a variety of reasons, 15 patients in the lorcainide group, and 12 in the placebo group withdrew from the follow-up, but not for any reasons that worried us.

Ambivalence about clinical trials

Perhaps more important than these reasons for ignoring the higher death rate in the lorcainide group was that I had been totally convinced by 'the siren call' of the clinical trial at this time. Trials were not then commonplace, as they became in the 1990s. Indeed, in 1983 I had argued that doctors should no longer have 'clinical freedom' to treat every patient as they saw fit, but rather should be forced to base their practice on the results of controlled trials.[10] New treatments and new technologies should not be introduced widely unless there was evidence from clinical trial evidence to support their adoption. This call was made a decade before the introduction of the now-hallowed term 'Evidence-Based Medicine',[11] and it has been one of my great regrets that I did not think of the phrase then.

Our lorcainide study faithfully followed all the rules of clinical trials as they were then understood. One of those rules was (and remains) that if differences are observed in outcomes that were not prespecified these should be regarded merely as generating hypotheses for testing in further studies. The difference in death rates following lorcainide and placebo had not been specified as a trial endpoint, so we felt entirely justified in ignoring it as likely to have reflected the play of chance.

On completing our study we tried to publish our results. Full of enthusiasm we started with *The Lancet* and then tried two or three cardiology journals. The result was always the same – immediate rejection. We lost interest, the company which produced lorcainide decided for commercial reasons (not because of our study) not to continue with the drug – and we forgot about it. In any case, the fashion had changed from arrhythmia suppression to clot busting (thrombolysis), and we were soon involved in the design and conduct of one of the first thrombolytic trials.

Thirteen years later, in 1993, I was beginning to lose my faith in clinical trials. They seemed to be chasing smaller and smaller benefits, often at the behest of the pharmaceutical industry. The patients included in trials were, perhaps inevitably, too highly screened, so that all of them would have only the disease under investigation. My patients, by contrast, always seemed to be older than the patients who had participated in the trials, and always seemed to have multiple diseases. It was difficult to know whether a particular drug's effects were due to its membership of a class of similar drugs, or from what might be its specific effect. This made drug and dose selection challenging. Trying to make sense of the published evidence, including the use of statistical synthesis of trial results (meta-analysis), often seemed to add apples to pears and then claiming an effect of fruit.

Publication bias

At the time, the term 'publication bias' was beginning to appear in the journals,[12] suggesting that the clinical research community was serving up for publication a biased sample of their research. At a coffee break in 1993, someone remembered our old lorcainide study and we realised that it was a perfect example of many of the failings of clinical trials. I suppose we had always felt that we had a moral duty to publish it. It had started with fashion – the belief that suppression of arrhythmias would reduce mortality after myocardial infarction – and it had ended with fashion when we lost interest in arrhythmias and turned to thrombolysis. And our strict adherence to our trial protocol may have blinded us to the importance of unwanted drug effects.

We cannot know whether the increased death rate in patients treated with lorcainide in our study was due to an effect of the drug or an effect of chance. In retrospect, it seems likely to have been an effect of the drug. In 1988, a systematic review of 14 trials of anti-arrhythmic trials[13] found that the odds of early death were about one-third greater among patients allocated drug than among those allocated placebo, although this difference was not statistically significant (95% confidence interval: 2% reduction to 95% increase). A systematic review of eight trials done in hospitals reported the following year showed a statistically significant greater mortality after administering anti-arrhythmic drugs.[14]

The conclusions of these systematic reviews would have been strengthened further had the results of our lorcainide trial been available for inclusion in them, and this would have amplified the early warning of the evidence of harm provided in the CAST studies.[1,2] But even before these large trials were reported, the results of cumulative meta-analysis of previous anti-arrhythmic trials could have helped avoid tens of thousands of unnecessarily early deaths.[15,16]

By the early 1990s, I was interested as much in trial methodology from the practising doctor's point of view as in trial results, so we tried again to get a report of our lorcainide trial published. Again, the high-impact factor journals were not interested. It was perhaps as a final throw of the dice that we added the words 'publication bias' to the title, and so finally found a home for the paper.[17]

The moral of this story is that evidence-based medicine often depends on evidence that has been collected according to the fashion of the day. It depends on what can be funded and on what interests journal editors and reviewers, and this too is often a matter of fashion. Perhaps we should talk about 'opinion-based' or 'fashion-based' rather than evidence-based medicine.[18] Translating the results of clinical trials to routine practice in individual patients who never seem to fit trial inclusion criteria is hard enough without also having to be slaves to fashion.

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