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Systematic reviews of animal experiments

The axiom “before testing a new treatment in man, test it first in animals if possible” has been part of drug development for the past 50 years or so. Testing in animal models is believed to increase the chances of identifying drugs that are sufficiently promising to justify the effort and expense of further clinical development. However, a recent study of the process of testing a potential treatment for acute stroke suggests that the relation between animal experiments and clinical trials is not so straightforward.

J Horn and colleagues did two systematic reviews of the effects of nimodipine in focal cerebral ischaemia. The first systematic review was of clinical trials of nimodipine for acute ischaemic stroke. They included data from 6468 patients in 22 trials of nimodipine. There were sufficient data to reliably rule out a clinically important effect.^{1,2} The investigators then went on to systematically review the animal experiments on nimodipine for focal cerebral ischaemia to see whether or not the animal evidence supported the starting of clinical trials in human beings.³ The results were surprising. There was no convincing evidence to substantiate the decision to start clinical trials and, furthermore, the animal experiments and clinical trials ran simultaneously.³

Systematic reviews allow for a more objective appraisal of the research evidence than do narrative reviews and by increasing the precision of estimates of treatment effects, systematic reviews can reduce the probability of misleading results. Over the past decade there has been a steady increase in the number of published systematic reviews and many funding bodies, including the UK Medical Research Council, now require a systematic review of the existing clinical trials before they will consider funding a new trial. However, systematic reviews of animal experiments are rare.

About one in every 1000 MEDLINE records about human research is tagged as a meta-analysis compared with one in 10 000 records about animal research.⁴ Had the systematic review of the animal experiments of nimodipine in cerebral ischaemia been available to the nimodipine investigators, would the total of 22 ultimately futile clinical trials of nimodipine still have been started? Assembling earlier a proper synthesis of the evidence—both animal and human—might have spared some of the 6400 or so patients in the nimodipine trials the risk and inconvenience of taking part in trials for which the rationale was questionable. Such unnecessary research is not ethical, and sponsors, trialists, and ethical committees will have to be vigilant in future to reduce the risk of such studies being initiated. Unfortunately, expertise in systematic reviews may not be prevalent in the basic science community or the pharmaceutical industry. The

cost savings to the pharmaceutical companies concerned could also have been substantial.

A second important observation from the systematic review of animal experiments by Horn and colleagues³ was that the methodological quality of the included animal studies was poor. It seems natural to insist that animal research should be subject to the same rigorous scientific methods used in clinical trials in human beings, yet such a point is sometimes viewed as controversial.⁵ Methodological issues that have been found to be important in clinical trials, such as allocation concealment and blinding of outcome assessment,⁵ were neglected in many of the animal experiments identified by Horn and colleagues. Systematic reviews of clinical trials were instrumental in helping methodologists to identify the determinants of bias in individual trials and to assess the impact of publication bias and other selection biases when making inferences on the totality of available evidence. Similarly, systematic reviews of the animal data have the potential to provide important insights into the determinants of bias in animal experiments.

Even a high-quality systematic review of high-quality animal experiments will only inform the conduct of human clinical trials if the results from animal experiments can be generalised to human beings. Again, research syntheses can help. Systematic reviews of animal experiments might include a range of different animal species and models. Consistent results across species and models would provide some reassurance that human beings might respond in the same way. Since the primary aim of animal experimentation is to inform about effects in human beings, information about whether results in animals can be generalised is particularly valuable.

It is well established that systematic reviews of the existing clinical trial evidence are prerequisites for the scientific and ethical design of new controlled trials. The results by Horn and colleagues suggest that systematic reviews of the relevant animal experiments need to be added as a prerequisite to the design of new clinical trials. Early in the development of the Cochrane Collaboration, Iain Chalmers predicted that “when the research community synthesises existing evidence thoroughly, it is certain that a substantial proportion of current notions about the effects of healthcare will be changed”.⁶ His predictions have proved accurate. Would our therapeutic notions also be changed if we systematically synthesised the results of animal research?

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