

Infrared ear thermometry versus rectal thermometry in children

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The precise and accurate measurement of core temperature helps in the confirmation or exclusion of fever. No routinely used site for core temperature is completely reliable for estimating core temperature. The rectal route has traditionally been the reference standard for measurement of core temperature,¹⁻³ despite being uncomfortable and unpopular for both patient and parents; the rectal site may also be slow to respond to rapidly changing core temperatures.⁴

There is wide agreement between temperatures measured at the axilla, the rectum, and the tympanic membrane, although temperatures taken from the tympanic membrane are less accurate than those measured in the pulmonary artery.^{1,4} Milewski and colleagues⁴ showed that rectal temperatures in adults correlate more closely with pulmonary artery readings than tympanic measurements, although others¹ contend that tympanic temperatures are more reflective of core temperatures than the temperatures obtained from the rectal or axillary sites.¹ Over the past 15 years, the use of infrared tympanic thermometry has become more popular in both hospital and community practice with about two-thirds of paediatricians and family-health physicians using tympanic thermometers.^{5,6} Tympanic temperatures correlate well with temperatures taken simultaneously from the oesophagus and rectum.¹

Although many studies have attested to the reliability and popularity of tympanic thermometry,^{7,8} other studies have expressed concerns about accuracy.⁹⁻¹¹ Some investigators showed that the tympanic temperatures differed from true rectal temperatures by over 0.3°C in between 26 and 62% of patients and by over 0.6°C in about a third of patients.^{7,11} The upper and lower limits of agreement between temperatures recorded at the rectum and ear canal can be as wide as +3°C and -1.2°C in simultaneous recordings,⁷ while the corresponding variability for tympanic and axillary temperature was between +2.49°C and -0.74°C.¹² The ability of tympanic thermometry to detect or exclude pyrexia ranged from 88.9% to 98.2%.⁷ It has also been suggested that there is need to exercise caution in the use of the rectum as a reference standard, since the anatomical position of the tympanic membrane is superior to the rectum because of the proximity of the tympanic membrane to the blood bathing the hypothalamus which represents the true core temperature.²

In this issue of *The Lancet*, Jean Craig and colleagues, in a systematic review, showed a pooled mean difference between the rectal and tympanic temperatures of 0.29°C (95% CI -0.74 to 1.32). The investigators, however, conclude that infrared tympanic thermometry does not show sufficient agreement with the other methods because of the wide variability in measurement. The wide variability in these results implies false-high and false-low temperatures, which will have serious implications for management because the readings may lead to unjustified reassurance or unnecessary intervention. However, a recent study⁷ showed utility, accuracy, and reliability of tympanic thermometry, and few false-negative or false-positive results with a smaller mean difference of -0.09°C (0.13 to 0.05) and a high concordance of 0.832 (0.801 to 0.864) between aural and rectal temperatures.

What should be the interpretation of the results so far? The wide variability between studies and the poor degree of agreement in the systematic review by Craig and

colleagues between aural and rectal temperatures may be largely methodical. The meta-analysis may have been affected by different methods in the studies, and it might have been difficult to control for quality of instrumentation and technique. Although tympanic thermometry is acceptable to patients, parents, and healthcare practitioners,¹³ it is not yet clear that tympanic thermometry is sufficiently accurate to measure core temperature.^{9-11,14}

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Opportunistic infections in HIV-infected individuals: hepatitis C virus

The therapeutic successes of antiretroviral therapy for the treatment of HIV infection have profoundly altered the importance of hepatitis C virus (HCV) infection in HIV-infected individuals. From the epidemiological perspective, a third to a half of the HIV-infected individuals in industrialised countries are HCV/HIV coinfecting.¹ Clinically, prospective studies in cohorts of patients with haemophilia have shown that the incidence of end-stage liver disease and hepatocellular carcinoma are increased in HIV/HCV coinfecting individuals compared with mono-infected individuals.^{2,3} Histologically, several epidemiological studies have suggested that hepatic fibrosis, the main cause of morbidity and mortality from HCV-infection, is increased two-fold in HIV/HCV coinfecting individuals.^{4,5}

A multinational task force recently made recommendations for the management and treatment of HCV in HIV/HCV coinfecting individuals.⁶ Several of the guidelines are a reaffirmation of those published elsewhere. For example, the recognition of the prominence of HCV as a pathogen in HIV-infected individuals led the US Public Health Service and the Infectious Disease Society of America to issue guidelines recommending that all HIV-infected individuals should be screened for HCV infection.⁷ Individuals who test positive for antibodies to HCV should be treated, if indicated. Currently, evaluation consists of the determination of active HCV infection, as indicated by the presence of detectable HCV RNA in serum, the determination of HCV genotype, abdominal ultrasound, and liver biopsy. The usefulness of the liver biopsy, which is necessary to judge the degree of necroinflammatory activity and the amount of fibrosis, was recently confirmed by the US National Institutes of Health Consensus Conference on HCV.⁸

The treatment of HCV has evolved from interferon monotherapy to treatment with the combination of pegylated interferon and ribavirin. Pegylated interferon, the conjugation of interferon with polyethylene glycol, results in a longer-acting compound that has recently become the standard of care for the treatment of HCV.^{9,10} With these agents, viral eradication is possible in about 50% of HCV-monoinfected individuals. Trials with these agents are ongoing in HCV/HIV-coinfecting individuals. Interim analysis of ACTG trial A5071 revealed that only 44% of coinfecting individuals responded to pegylated interferon plus ribavirin at 24 weeks,¹¹ which is less than the overall sustained virological response of 54% in HCV-monoinfected individuals.⁹

The immunomodulatory effects of interferon and ribavirin are thought to be a principal reason for their therapeutic efficacy. Interferon promotes the immune response against HCV¹² and ribavirin is thought to enhance the Th1 immune response.¹³ Consequently, the immune status of the coinfecting individual may be an important consideration in the therapeutic goal of HCV eradication, a goal that may be easier to achieve in individuals with well-preserved CD4 cell-counts.¹⁴ Among individuals with lower CD4 cell-counts, a benefit that may accrue is a reduction in the rate of progressive liver disease, even in the absence of viral eradication. The same goal provides a rationale for the current interest in maintenance therapy for HCV both in monoinfected and in coinfecting individuals. Interferon can result in a dose-dependent decrease in the CD4 cell-count that has resulted in AIDS-defining opportunistic infections.¹⁵ Therefore, a CD4 count below 100 cells per μL is a relative contraindication for interferon treatment and antiretroviral therapy should be the priority in these individuals at least until the CD4 counts improve.

Management of side-effects of anti-HCV therapy, which may be more severe in HIV/HCV coinfecting individuals, is important too. The main haematological side-effects of neutropenia (with interferon) and anaemia (with ribavirin) may be more severe in HIV-infected individuals in whom antiretroviral therapy and HIV may contribute to bone-marrow suppression. These side-effects can be treated successfully with erythropoietin and granulocyte-colony-stimulating factor. In addition, co-existing psychiatric conditions, including alcohol and substance abuse, should be evaluated before and closely monitored during therapy. Depression, another common side-effect of interferon, should be treated aggressively.

Although most studies agree that HIV has a deleterious effect on HCV infection, the effect of HCV on the course of HIV is controversial. Mark Sulkowski and colleagues,¹⁶ in a recent study in an urban cohort from the USA, show that HCV infection does not substantially alter the chances of an immunological response to antiretroviral therapy, developing AIDS, or dying.¹⁶ Conversely, data from a large cohort of HIV-infected individuals in Switzerland demonstrate that HCV seropositivity increases the likelihood of progressing to AIDS-defining illness and death during a median follow-up of 28 months.¹⁷ Whether demographic differences between these populations can account for the discordant results will require further investigation.

With the reduction in HIV-attributable morbidity and mortality because of antiretroviral therapy, new pathogens are becoming prominent in HIV-infected individuals. From epidemiological, clinical, virological, and histological perspectives, HCV is of particular importance. With the current range of antiviral agents, the potential efficacy of anti-HCV therapy in HIV/HCV coinfecting individuals adds hope to the already dramatic improvement that has occurred in HIV-attributable morbidity and mortality. For those individuals who cannot be treated with currently available agents, many new therapeutic agents (many specifically targeted toward HCV) will become available during the next 3 to 5 years.

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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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