The death of a volunteer research subject: lessons to be learned

Richard Ian Ogilvie

A healthy 24-year-old woman died in June 2001 following participation in a research protocol involving the administration of hexamethonium bromide by inhalation and methacholine challenge.[1] She was the third volunteer in a clinical trial at the Johns Hopkins Asthma and Allergy Center designed to test the hypothesis that local ganglionic blockade would suppress the bronchial protective effects of deep respiration presumed to be mediated by nonadrenergic, noncholinergic nerves releasing nitric oxide. (Normally following a period of quiet breathing, a deep breath is able to protect the airways from stimuli that cause bronchoconstriction. In people with asthma, the allergic reaction may partially disable the bronchodilator effect of deep respiration. The research protocol was designed to test whether blocking the ganglionic nerve transmission in normal lungs with hexamethonium would mimic the asthmatic response to a deep breath.) The day after being given the hexamethonium, the volunteer experienced a cough and dyspnea followed by flu-like symptoms, fever, reduced FEV_1, pulmonary infiltrates, adult respiratory distress syndrome with progressive hypotension and multiple organ failure. Autopsy revealed no specific cause for the lung damage. The woman had been a technician at another laboratory at the centre that gave time off work for the experiments in addition to the usual modest honorarium.

Internal and external review panels issued reports[1] that should be required reading for all clinical researchers. Research ethics boards (REBs) and regulatory agencies, hospitals and universities will probably be reviewing many of their policies and procedures to ensure the safety of all clinical trial participants, whether healthy volunteers or patients, and the disclosure of all risks before consent is obtained.

In the hexamethonium study, safety could have been improved. First, the chemical solution was not prepared by a pharmacist, and the protocol for preparation and delivery by nebulization was altered during the course of investigating the first 2 volunteers. The possible lack of sterility and enhancement of drug delivery could have compromised safety. Second, the first volunteer experienced a cough and dyspnea with deep breathing and exertion as well as reductions in measured lung function for 1 week following the hexamethonium inhalation. Without completely assessing other possibilities or discussing the event with the REB, a safety monitoring group or other researchers who had used hexamethonium inhalation, the researcher concluded that the episode was probably due to a concurrent viral infection. In hindsight, such discussions might have delayed or prevented administration of the drug to the third volunteer. Third, use of the sitting rather than the standing position to measure hemodynamic changes could have resulted in a greater blockade than achieved in previous reports.[2–5] The only feasible way of assessing the completeness of ganglionic blockade is by defining the orthostatic reduction in systolic blood pressure and increase in heart rate. Postural change from lying to sitting rather than to standing may blunt the response, which would give the impression that insufficient hexamethonium had been administered.

Another component of the trial that could have been improved was the consent form. It failed to indicate that hexamethonium was not an approved drug for clinical use and had never been approved for delivery by inhalation in the United States. Risks known to the researcher were not disclosed, and it is apparent that the researcher had not carefully searched the literature and was himself unaware of some of the risks. In his study protocol the researcher cited 4 reports of studies in which inhaled hexamethonium had been given to 20 subjects without adverse events. Discussions within the medical community subsequent to the volunteer's death have unearthed an unpublished report of a possible pulmonary complication experienced by a healthy volunteer in a 1978 study in San Francisco after receiving hexamethonium by inhalation. A possible association with pulmonary toxicity was not considered until the third volunteer was admitted to hospital, when the researcher found a Web site (www.pneumotox.com) that suggested a relation to longer-term use of ganglionic blockade for the treatment of hypertension.

The Johns Hopkins investigators into this tragic event found additional reports of pulmonary toxicity published between 1953 and 1962,[6–16] including a 1955 article in *CMAJ*,[10] and a review article published in 1972[17] that were not included in the protocol submitted to the REB. Neither of the review panels felt that this information would have stopped the trial.

Could this or a similar event have occurred in Canada? Most observers would admit that it is possible, for many reasons. Volunteer members of REBs are overburdened with too many complicated protocols and pressure from researchers and outside sponsors for rapid review. Researchers may underemphasize possible adverse events in order to achieve consent. The pharmacological knowledge

of medical graduates seems to have decreased over the past decade or so. Formal courses in pharmacology have been abandoned, and there are few clinical pharmacologists to ensure graduate and postgraduate expertise. Most REBs do not have clinical pharmacologists or clinical pharmacists as members to review protocols involving chemical entities. Current literature search techniques often emphasize references from the past 15–20 years at most. Older literature is often overlooked. Reports of adverse effects during clinical trials may not get published, as was the case of the hexamethonium inhalation toxicity in the 1978 San Francisco study. REBs do not have the personnel to conduct continuing reviews of clinical trials.[18] Researchers, not pharmacists, often prepare and administer investigational drugs.

In Canada, there are specific rules similar to those in the United States that govern applications for permissions to conduct clinical trials. Sponsors must file a clinical trial application for phase I, II and III trials of unapproved drugs and for trials of marketed drugs whose proposed use falls outside of the approved use of the drug (e.g., changes in indications and clinical use, target patient population, route of administration and dosage regimen). Phase I trials include those in which new drugs are used as research tools to explore biological phenomena or disease processes. Hexamethonium bromide is such a drug, and thus a Canadian researcher would be obliged to make an application to use it. However, it is unclear whether a similar requirement is in place in the United States. As part of the application process in Canada, the appropriate department head of the institution where the researcher is employed would have to sign the application, which would imply that a departmental review has occurred. Unfortunately, institutions do not always conduct this review and instead rely on the REB approval mechanism. Applications must also include data on product quality and manufacturing. Not all institutions have a research pharmacist for the preparation, storage, distribution or administration of investigational drugs. In my opinion, the procedures in use in Canada to ensure high levels of safety and fully informed consent are no better than those in place in the United States. A similar event could just as well occur in this country.

The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*[19] guides the composition and mandates of Canadian REBs, including procedures for monitoring clinical research. It recommends the proportionate approach to ethics assessment so that trials involving healthy volunteers given an unapproved drug such as hexamethonium by an unusual route of inhalation would be considered high risk. In my view, this should prompt an REB to perform an additional review of the consent process and to establish a safety monitoring committee. There would be need for special attention to eliminate all possible coercion of volunteers. Despite all of these measures, however, serious adverse events may still occur.

There are many lessons to be learned from the volunteer's unfortunate death. Some changes are being made. In January 2000 Health Canada published clinical trial regulations that clarified the conduct of clinical trials as well as the role and responsibilities of REBs. They are currently undergoing review and may yet be modified.[20,21] The National Council on Ethics in Human Research has been working assiduously to improve the ethical review of clinical research since 1989 and is actively promoting voluntary accreditation of REBs with increased resources and training for their activities.[22] The Canadian Institutes of Health Research considers ethics to be a major accountability issue for its credibility (www.cihr.ca/about_cihr/ethics/ethics_menu_e.shtml). The voluntary, nonprofit organization, Canadians for Health Research (www.chrcrm.org), continues to inform the public at large of ethical issues.

However, in the final analysis, it will be implementation of these rules for conducting clinical trials and ensuring the safety of participants that will be most important. I believe that particular emphasis should be placed on clinical trials using drugs as pharmacological tools. Departmental or institutional review as well as REB review of protocols should always be undertaken, with enhanced review of protocols by experts in pharmacology and pharmacy, additional review of the consent process when healthy volunteers are enrolled and establishment of safety monitoring committees for high-risk protocols.

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References

1. Research volunteer death [links to related documents]. Baltimore: Johns Hopkins Medicine. Available: www.hopkinsmedicine.org/researchvolunteerdeath.html (accessed 2001 Oct 12).
2. Holltzman MJ, Sheller JR, Dimeo M, Nadel JA, Boushey HA. Effect of ganglionic blockade on bronchial reactivity in atopic subjects. *Am Rev Respir Dis* 1980;122:17-25.
3. O'Bryne PM, Thomson NC, Latimer KM, Roberts RS, Morris MM, Daniel ED, Hargreave FE. The effect of inhaled hexamethonium bromide and atropine sulphate on airway responsiveness to histamine. *J Allergy Clin Immunol* 1985;76:97-103.
4. Sterk PJ, Daniel EE, Zamel N, Hargreave FE. Limited maximal airway narrowing in non-asthmatic subjects: role of neural control and prostaglandin release. *Am Rev Respir Dis* 1985;132:865-70.
5. Ichinose M, Inoue H, Miura M, Takishima T. Non-adrenergic bronchodilation in normal subjects. *Am Rev Respir Dis* 1988;138:31-4.
6. Morrison B. Parenteral hexamethonium in hypertension. *BMJ* 1953;1:1291-9.
7. Morrow JD, Schroeder JA, Perry HM Jr. Studies on the control of hypertension by Hyphex II toxic reactions and side effects. *Circulation* 1953;8:829-39.
8. Corcoran AC, Dustan HP, Taylor RD, Page IH. Management of hypertensive disease. *Am J Med* 1954;17:383-94.
9. Doniach I, Morrison B, Steiner RE. Lung changes during hexamethonium therapy for hypertension. *Br Heart J* 1954;16:101-8.
10. Robillard R, Riopelle JL, Adamkiewicz L, Tremblay G, Genest G. Pulmonary complications during treatment with hexamethonium. *CMAJ* 1955;72:448-51.
11. Goldsmith HJ, Beaven DW, Kambert HP. Severe hypertension treated with hexamethonium bromide in retard medium. *Lancet* 1955;1:371-4.
12. Perry HM Jr., O'Neil RM, Thomas WA. Pulmonary disease following chemical ganglionic blockade: a clinical and pathological study. *Am J Med* 1957;22:37-50.
13. Hildeen T, Krogsgaard AR, Vimptrup BJ. Fatal pulmonary changes during medical treatment of malignant hypertension. *Lancet* 1958;2:830-2.
14. Petersen AG, Dodge M, Helwig FC. Pulmonary change associated with hexamethonium therapy. *Arch Intern Med* 1959;103:285-8.
15. Rokseth R, Storstein O. Pulmonary complications during mecamylamine therapy. *Acta Med Scand* 1960;167:23-7.

16. Heard BE. Fibrous healing of old iatrogenic pulmonary oedema ("hexamethonium lung"). *J Pathol Bacteriol* 1962;83: 159-64.
17. Rosenow EC. The spectrum of drug-induced pulmonary disease. *Ann Intern Med* 1972;77:977-91.
18. Weijer C. Continuing review of research approved by Canadian research ethics boards. *CMAJ* 2001;164(9):1305-6. Available: www.cma.ca/cmaj/vol-164/issue-9/1305.asp
19. Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. *Tri-council policy statement: ethical conduct for research involving humans*. Ottawa: Minister of Supply and Services; 1998.
20. Minister Rock announces approved amendments to Canada's Food and Drug Regulations — clinical trials [press release]. Ottawa: Health Canada; 2001 June 20. Available: www.hc-sc.gc.ca/english/archives/releases/2001/2001_69e.htm (accessed 2001 Oct 16).
21. Regulatory amendments to clinical trial framework [information sheet]. Ottawa: Health Canada; June 2001. Available: www.hc-sc.gc.ca/english/archives/releases/2001/2001_69ebk2.htm (accessed 2001 Oct 16).
22. Dinsdale H. The accreditation of Canadian REBs. In: *Proceedings from the NCEHR national workshop, March 25-26, 2001*. Ottawa: National Council on Ethics in Human Research. Available: www.ncehr-cnerh.org/english/mstr_frm.html (select "What's New" on main menu, then "Toronto workshop" under "Proceedings from the NCEHR National Workshop") (accessed 2001/10/15).

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