Ethical modifications of the Emergency Drug Release Program for AIDS: a proposal

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The clinical testing of promising new drugs and the subsequent federal licensing ensure a reasonable level of efficacy and safety. They are also considered necessary safeguards to prevent desperate patients from being manipulated into accepting the risks associated with unsubstantiated promises.[1]

Usually a physician who wants to use an unlicensed drug must obtain approval from the federal licensing and local institutional ethics authorities before the pharmaceutical company can release the drug. Occasionally such products can be released under "compassionate use" regulations: suspension of the usual protective mechanism of protocol review is allowable because the patient is in a desperate situation — typically, about to die. The physician must justify the release of the drug, and he or she retains prescribing authority. Little or no scientific information is gained from such a single use. Regardless of whether the risks of compassionate, experimental therapy are great or unknown they are assumed to be no more severe than those resulting from nontreatment.

Compassionate approval or emergency drug release is usually limited to one patient. If other patients require the drug a formal research protocol must be designed and submitted for review to ensure that ethical and scientific standards are met. The review is also necessary because the financial resources of hospitals and health insurance carriers often extend to meet supportive care and the monitoring of the risks associated with treatment given as part of a research protocol. For single use, however, such administrative commitments are not needed.

Compassionate release of drugs for AIDS

Because of the severe clinical course of acquired immunodeficiency syndrome (AIDS) and its associated opportunistic infections many patients have demanded access to drugs that are at the earliest stages of development. Regulators in Canada and the United States have responded to this demand by releasing, for compassionate reasons, drugs that have often received only preliminary clinical testing of their toxicity and optimum dose.[2,3] In Canada the release of some drugs has been restricted to formal clinical studies, but others are readily available on compassionate grounds under emergency drug regulations to any licensed physician. This expedited release of unproven drugs creates a complex set of ethical and administrative dilemmas.

Ethical considerations

The usual ethical justification for exposing patients to risk for unknown benefit is that data are being rigorously gathered for the safety and benefit of future patients. This cannot be said of drugs released compassionately to those with AIDS under the emergency drug regulations. Furthermore, the widespread availability of these drugs "off protocol" may deter patients from enrolling in controlled studies that could produce information on efficacy. When an agent receives widespread favourable publicity our experience suggests that there is a loss of accrual to controlled studies of the agent. Others' experience has been documented elsewhere.[3-7]

A patient's desire to receive an innovative therapy does not establish a right to do so,[4] nor does it override society's ethical obligation to balance access to therapy (even for desperate people) with safety and to evaluate such therapy for its efficacy and toxic effects.[3] Similarly, this desire does not establish a moral obligation that the costs of the treatment will be covered under Canada's health

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care plan. Society's duty to finance desired therapies exists only if the therapy is effective and may, therefore, be said to meet a need. Nevertheless, patients' wishes may be accommodated if this is done in a way that does not undermine the advancement of knowledge, expose the patient to unreasonable risk or incur unacceptable or unapproved costs.[4]

Administrative considerations

The current procedure for evaluating drugs released on a compassionate basis to more than one patient requires local evaluation of a formal study protocol, an appropriate informed consent procedure, financial disclosure and review by the research ethics board to determine scientific and ethical acceptability. New agents are being released regularly. For example, 13 new treatments for AIDS and its related infections were listed as available under the Emergency Drug Release Program in a November 1990 communication from the Health Protection Branch (HPB) of the Department of National Health and Welfare,[8] and others were being released under open protocols. Clearly the volume of such drugs imposes major ethical and administrative burdens on research ethics boards, prescribing physicians and third-party payers.[9] Furthermore, provincial health care plans are expected to provide appropriate supportive care and, for some patients, the cost of therapy.

In view of these considerations we propose a universal review protocol for new drugs to treat AIDS. The protocol would yield rigorous but streamlined ethical, scientific, administrative and financial reviews. The practical result would be that patients would have rapid access to experimental drugs with all the available data, physicians would be better supported in the prescribing and monitoring of the drugs, and costs would be explicitly identified for hospital research budgets and provincial insurance plans. By this means physicians and institutions would meet their moral and scientific obligations to patients and the advancement of knowledge.

Standardized compassionate release protocol for AIDS therapies

The protocol consists of universal and specific components.

Universal component

Physicians would submit the universal component for initial review to all relevant local administrative committees involved in experimental therapies. Its acceptance would constitute "standing" or "continuing" approval for the AIDS emergency drug release program, obviating the need for subsequent detailed review, except for substantive ethical, administrative or financial modifications.

The research team named in this component may have institutional and noninstitutional members, but it would form the only locally authorized prescribing group. This would guarantee a higher level of research expertise, more systematic collation of otherwise uncontrolled data in a cost-effective manner and safer and more expeditious access to clinical expertise about the diseases, the drugs and their alternatives.[10] In addition, limiting access to innovative drugs to authorized groups would permit relevant information to be provided to patients and shared more easily among centres. The prospect of information exchange and collation of data on patient recruitment would make pharmaceutical companies more likely to give focused financial support for such studies. A standardized protocol would also rationalize federal and provincial health care support for such drugs and improve patient access to them.

The submitted protocol should explain the rationale for the novel review procedure dictated by the changing regulatory emphasis in the United States and Canada. Specific physician collaborators involved in the care of patients with human immunodeficiency virus (HIV) infection or AIDS should be listed to document their ability and willingness to supervise the restricted use of the drugs. Participating physicians should make a formal commitment that patients would not be diverted from treatments that might be more effective and that the emergency release of a drug would not undermine recruitment to a local controlled trial.

A universal informed consent form (Fig. 1) must explain the rationale for the release of unlicensed drugs to treat HIV infection and emphasize that the benefits and toxic effects of unapproved therapies are unknown. Each patient's decision to accept an unproven drug should be taken only with the knowledge of his or her personal physician. The informed consent form should include a statement by the patient that the potential and known side effects have been explained orally and that a written patient information sheet has been provided.

Specific component

A drug-specific component of the protocol (Table 1) should be submitted for expedited review each time an unlicensed drug is made available for compassionate release under emergency drug regulations or is released for an open-label uncontrolled study or when the indications for the use of a previously licensed drug are modified. After review of the drug-specific component the chairperson or

CONSENT FORM

Research project: .....

Investigators: .....

Funding agency: .....

This consent form is only a part of the process of informed consent. It should give you the basic idea of what the research project is about and what your participation will involve. If you would like more details about anything, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

Most drugs are rigorously tested before they can be prescribed by physicians. Drugs for AIDS and HIV-related infections are an exception. Because these infections are so serious and because there is no known cure, some AIDS drugs can be used under special conditions before they have been thoroughly tested; however, their benefits and harmful effects are uncertain. You are encouraged to take the accompanying Drug Information Sheet to your personal physician to discuss whether you wish to take this medication.

Your illness, its course and its management will be explained to you; you will also be told about the untested treatments that are available. You will be given one or more drug information sheets along with a copy of this consent form for your records and for future reference.

The investigators should explain to you the information on the sheets in ordinary language, avoiding jargon and supplying explanations for important terms.

Please sign this form to show that you have understood the information about the research project and that you agree to be a subject in it. In no way does your signature affect your legal rights or release the investigators and others involved from their legal and professional responsibilities. You are free to withdraw from the study at any time and still receive regular health care. If you continue to take part in the project you should feel free to ask for information or clarification at any time. If you have further questions concerning this research please contact

..... [name of investigator or qualified designate]
..... [telephone number]

If you have any questions concerning your rights as a possible participant in this research please contact [e.g., the Office of Medical Bioethics, Faculty of Medicine, University of Calgary, telephone 220-7990].

.....
Name

.....
Signature (of subject or proxy, if applicable)

.....
Name of witness

.....
Signature

.....
Date

Fig. 1: Sample consent form for the standardized compassionate release protocol for AIDS therapies.

delegate of the research ethics board would be able to expedite the approval of the drug for immediate local use.

This part of the protocol should be brief but should include relevant data on the pharmacologic features of the drug, its recommended dosage, the known toxic effects and clinical indications, the inclusion and exclusion criteria, the rationale for use and the duration of therapy. These data should be summarized on the patient information sheet. The impact on the facility in terms of admission, drug cost, patient visits, laboratory monitoring for side effects, and duration of therapy should be included. For close monitoring of the drug's use a ceiling on the number of patients to be enrolled should be given for each drug.

Discussion

The Canadian response to patients' demands for new drugs has seen the transfer of the responsibilities of federal regulatory bodies to local committees, institutions and physicians. As well as evaluating the ethical and scientific validity of such therapies these local groups are often responsible for administrative and financial issues and for the protection of patients through an assessment of the treating physician's competence to use the therapies.

Physicians caring for HIV-infected patients who demand such drugs will inevitably feel compassion and an obligation to try every available treatment of any possible value. A full conventional review for each agent would be wasteful of the time and expertise of research ethics boards and might delay fast access to therapy. In effect, the absence of peer, ethical or administrative review fostered by widespread compassionate release might leave physicians who lack any university, hospital or community clinic affiliation morally and legally vulnerable or even resistant to using such treatment. The listing of physician collaborators in the universal protocol would identify appropriate avenues of referral and sources of education. It might also encourage unaffiliated physicians to collaborate with the primary investigators, depending on their patients' needs and their own levels of expertise.

The standardized compassionate release proposal would provide institutions with a mechanism to monitor the use of therapies provided for compassionate reasons. Most important, it would allow physicians to use therapies that have little, if any, administrative and financial support from a pharmaceutical sponsor and that have had little evaluation of safety and efficacy. By this procedure patients who are infected with HIV or who have AIDS would not be denied rapid access to innovative therapies,

Table 1: Information to be provided in the drug-specific component of the protocol

Major item	Specific information
Drug	Name or class
	Manufacturer or sponsor*
	Proposed mode of action
	Proposed pharmacologic features and regimen
	Toxic effects
	Indications
Study	Inclusion and exclusion criteria
	Duration of therapy
	Length of study
	Proposed monitoring†
	Need for research on specific drug
	Specific requirements of subjects
	Maximum enrolment
Facility resources‡	Name of facility paying for the drug
	Name of facility paying for supportive services
	Hospital admissions
	Outpatient visits
	Laboratory services
	External monitoring

*Attach any protocols provided by sponsor.
†Describe the monitoring usually required for this patient group and additional monitoring needed for this protocol.
‡The costs are those above the costs of routine care directly associated with the use of a new agent.

monitoring would likely be improved when conducted by integrated groups of physicians and research for more effective and safe treatments might progress in an environment more respectful to patients.

Conclusions

We believe that our proposal offers not only an efficient and cost-controlled approach to promoting compassionate care for patients with AIDS but also preserves the hope of improved care for future patients. This model may be immediately adopted by local institutions, or it could be made mandatory by the HPB.

The release of numerous new drugs under emergency drug regulations has been limited to AIDS, and we have discussed only this condition. However, if such releases become common for other medical conditions a national re-evaluation of "compassionate" therapeutics will become necessary. The compassionate release of drugs for HIV infection could become the paradigm process that corrodes and corrupts the ethical and scientific validation of new pharmaceuticals in Canada. The desperate situation of AIDS patients is not ethically different from that of other patients with untreatable, terminal conditions. If the compassionate release of drugs for terminally ill patients without AIDS is contemplated, a mechanism similar to the one we have proposed will be required to ensure patient protection and the facilitation of responsible research.

We thank Stella Massey-Hicks and Lynda Gourlie for their secretarial assistance.

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