The Impact of Ethics on the Design and Conduct of Acupuncture Clinical Trials

Christopher Zaslawski [1, *]

[1] Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research, Hyderabad (NIPER-H), Balanagar, Hyderabad 500037 Telangana, India

[2] National Center for Mass Spectrometry, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500607 Telangana, India

[3] Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Hyderabad (NIPER-H), Balanagar, Hyderabad 500037 Telangana, India
* Corresponding Author. E-mail: srini@iict.res.in

Abstract. Racecadotril, an enkephalinase inhibitor, was subjected to hydrolysis (acidic and alkaline), oxidation, photolysis and thermal stress, as per ICH specified conditions. The drug showed extensive degradation under acidic, basic hydrolysis and oxidative stress conditions whereas, it was stable under other stress conditions. A total of seven degradation products (DPs) were observed. The chromatographic separation was optimized on Acquity HSS Cyano (100 × 2.1 mm, 1.8 µ) column using 0.1% formic acid and acetonitrile as mobile phase in gradient mode. Six DPs were characterised by LC–MS/MS and DP1 by GC–MS. The major DPs (DP 2 and DP 5) were isolated and characterised by NMR. This is a typical case of degradation where co solvent methanol reacts with racecadotril leading to the formation of pseudo DPs, DP 6 and DP 5. Interestingly the MS/MS spectra of protonated drug, DP 4 and DP 7 showed product ions which were formed due to intramolecular benzyl migrations. In vitro cytotoxic activity studies on isolated DP 2 and DP 5 revealed that the former has no cytotoxic nature, whereas the latter has potential pulmonary and hepatic toxicity.

Keywords: Forced degradation; LC–MS/MS; Benzyl-benzyl interactions; GC–MS; Cytotoxic assay.

1. Introduction

The consideration of bioethics is an integral process in the design and conduct of a clinical trial. Currently, peer reviewed journals require a statement that the submitted research has been assessed and approved by an institutional review board. Researchers often overlook ethical issues until they are required to submit such an application for approval. While there may have been an implicit understanding and acknowledgment of ethical issues, the application process can help clarify issues and may lead to consideration of different design options. Furthermore, ethical issues often arise during the conduct of research and therefore a discussion on the contribution of ethics to acupuncture research seems additionally warranted. This paper will outline some general issues associated with ethical research and how they may impinge on the design and implementation of acupuncture research.

2. Ethics and health research

Western medical ethics arose from the clinical practice of medicine and had its ethical origins in the Hippocratic code that sought to regulate the practice of its practitioners. During the development of medicine the focus of ethics shifted to medical etiquette, with the development of customs relating to dealing with patients and other practitioners. Practitioners were often loath to reveal their treatment and there was reluctance amongst them to criticise one another.1

Following the Nuremberg trials of 1946, the ethical principles for human experimentation were defined in what was known as the Nuremberg code. It arose from the abuse of medical research in the

Nazi concentration camps. This was later incorporated into the World Medical Association (WMA) Declaration of Helsinki that was to form the basis for the development of guidelines for human experimentation.2 Since its adoption in 1964 by the WMA, it has undergone a number of revisions, the most recent being in 2000.3 As clinical research accelerated, many institutions in the 1960s and 70s looked to the establishment of institutional review boards. They used the Declaration of Helsinki as a basis for evaluating ethical issues such as informed consent, protection from harm, weighting of hazards and benefits, coercion to participate, and the protection of the subject's privacy.

Chinese Medicine also had its ethical codes of practice whereby illness was seen as arising from a departure from laws of nature and society. Confucianism especially, with its emphasis of human relations and obligations towards fellow human beings, had a definite influence on the development of ancient medical ethics.4 With the spread of Chinese medicine to the West, the development of ethical concerns has continued, especially in relation to professional practice ethics in a Western society.5

As a profession, acupuncturists are being called to validate their claim that acupuncture has therapeutic value. They are ethically bound as a group, to respond to the request by designing and participating in methodologically sound clinical research. It would be unethical to dismiss the request and continue to offer treatment based on unsubstantiated claims that have not been externally validated.6 In addition, researchers are ethically obliged to improve upon and develop new methods of treatment. The Declaration of Helsinki3 clearly identifies the need to investigate scientifically unproven practices such as acupuncture, that nevertheless have a long history of clinical success.

> In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published.

3. Institutional review boards

Institutional Review Boards (IRB) or Human Research Ethics Committees as they are termed in the United States, were established to ensure that all research undertaken by staff and students of an institution conform to the highest ethical standards. The three fundamental principles underlying the ethical administration of research are respect of persons, respect for justice and beneficence.7 The role of the IRB extends to protect not only the interests of the participants of the research, but also the researchers and the institution. With the introduction of acupuncture into higher education and the increasing attraction for acupuncture practitioners to undertake research, the need to understand the ethical concerns of research and the process of gaining ethical approval is imperative. Furthermore, novice researchers can gain an understanding of the issues that confront the IRB when an acupuncture research proposal is submitted, while the IRB can gain an understanding of the peculiar ethics that may be associated with acupuncture research methodology when an application is evaluated. This last point is especially relevant when many IRBs may not have had experience with evaluating acupuncture proposals and may turn down a good proposal because they fail to understand the methodology, or the terminology, in the application. It is incumbent on the acupuncture researchers, whether they are novices or experienced researchers, to make sure their application has every opportunity to be approved. IRB members come from a wide variety of backgrounds and often include members of the public. It is therefore necessary to communicate in plain simple language free from jargon. Technical terminology should be kept to a minimum and a glossary provided if necessary. On the other hand, the IRB will also include experienced researchers who may be unfamiliar with or biased against acupuncture, and it is important that the application communicates in terms they are familiar with. Chinese medicine terms should be limited and clearly defined or alternative expressions found. For example the acupuncture term deqi could be replaced by the term needling sensation.

Another possible barrier to acupuncture research, especially for independent acupuncture colleges, could be the lack of access to a IRB. The Declaration of Helsinki3 clearly directs that all research should be channelled through a IRB for ethical consideration.

> This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The submission of a research application to a IRB is obviously a problem for small acupuncture colleges who are not affiliated with orthodox institutions and do not have the resources or infrastructure to establish a IRB. The most obvious solution would be to collaborate with established researchers who are linked to an institution, such as a hospital or University, that do have an established IRB. Another option would be to approach a IRB independently. The IRB may be willing to assess a proposal and monitor the research for a fee. This may lead to future research collaboration with future research. A third, less attractive option, would be to establish an IRB. At the University of Technology, Sydney (UTS) where the author resides, a small IRB was formed to assess independent undergraduate research projects. The larger institutional (UTS) IRB was kept informed of the process and any dubious ethical issues brought to their attention. When pursuing this option, the IRB administrator at the local larger institution, may well be willing to help train the IRB being established at the acupuncture college. The advantage is that an acupuncture college based IRB is likely to become more knowledgeable in basic concepts of Chinese medicine in a shorter period of time, as well as being more sensitive to design issues that are particularly relevant to acupuncture research.

4. Developing an ethical research agenda

It is also important to consider how research will impact on community health and the contribution that the research will make to the discipline. Research needs to have outcomes that have significance for both the field of research and the wider community. The identification of diseases or illnesses that are in need of better therapies, and which acupuncture has been seen as a viable but untested treatment option, is a necessary first step in establishing a research agenda.8 Edwards9 has suggested that the prospective researcher needs to reflect on such issues. Why are we doing the research? Are we using systematic investigations designed to develop and contribute to the knowledge in the field? What will it produce for the investment? What will it contribute to the consumers of the research? Reflective questions such as these focus on the ethical heart of research. Researchers who are unable to give a satisfactory answer to such questions need to re-evaluate their goals and consider the health of the community, as well as their own interests.

IRBs also require that the research methodology is the most appropriate for the project and that it addresses the research question in a scientific manner. The adoption of a systematic research protocol, such as the US Food and Drug Administration (FDA) approach to clinical trials, allows the research team to develop the most appropriate and rigorous methodology for the research area.10 Given the high financial and human costs associated with implementing a clinical trial, it is imperative that the limited research resources are utilised in an ethical manner.[11] and [12] To proceed to a large-scale phase III clinical trial without some evidence or understanding of the research issues should be considered unethical, as well as a potentially wasteful venture.

5 . Ethical constraints associated with methodology

Constraints regarding acupuncture methodology, such as the difficulty of double blinding and the choice of a control, need to be identified and communicated to the IRB. The difficulty of double

blinding in an acupuncture trial has been well recognised yet IRB members may have little understanding of this issue which may lead to rejection of the application.13 Strategies to overcome the problems associated with single blinding may include minimizing bias by limiting or standardizing interaction, and blinding assessors. The strategies need to be made explicit when writing the application.10

The issue of whether or not to use a placebo control treatment and under what circumstances remains a vexing ethical issue.[14], [15] and [16] Rothman17 in reviewing the ethical concerns associated with the use of a placebo argues that

> 'every patient-including those of a control group, if any- should be assured of the best proven diagnostic and therapeutic method.' This statement effectively proscribes the use of a placebo as control when a 'proven' therapeutic method exists. The declaration [of Helsinki] also directs that a study that violates its precepts should not be accepted for publication… there is no straightforward way to estimate how many trials are undertaken that involve the unethical use of placebos.

This raises some interesting questions concerning the use of a placebo in acupuncture research. For example, it seems reasonable and ethical to demonstrate that the efficacy of acupuncture is not entirely due to the placebo effect. Conversely, it may not be ethical to treat a group of ill or diseased subjects with a placebo, despite them having given informed consent.

Hammerschlag15 in reviewing the ethical concerns associated with acupuncture control treatments classified the control options into five categories. The no treatment control (either wait list or no treatment) involves either delaying or denying of acupuncture treatment. The ethical issue associated with this option is the concern of whether the delay or denial of treatment would have a critical impact on the disease process. If the disease is greatly affected by the delay or denial of treatment then this method of control could be seen as ethically dubios. If however, the delay or denial of treatment had minimal effect on the disease, in other words the disease was of a stable and chronic nature, the ethical concerns would be minimal. A possible strategy to circumvent the issue would be to offer treatment, acupuncture if the outcome was positive, or standard medical care if the outcome was negative, after completion of data collection.

The second category, the acupuncture versus biomedical care model, was seen as being ethical in that there is an 'intent to treat' all subjects in the trial. This means that in both treatment arms, the acupuncture and the standard care, there was intent to treat the subject. However as acupuncture could be seen as an experimental procedure, the intent to treat does not necessarily equate to receiving appropriate treatment. Again, as in the no treatment category, either standard care or a course of acupuncture could be offered to the subject on completion of the trial. The issue of the delay or denial of treatment in the acupuncture group is also present in this model.

The third category was the acupuncture plus standard care versus standard care only model. This is the most ethical of the five control options in that there is no attempt to deny subjects effective, or partially effective, standard treatment. Fundamental to this approach is the recognition that the standard treatment has been previously validated as an effective or partially effective treatment. The 'intent to treat' is common to both groups.

The next two categories, acupuncture versus placebo (non-invasive treatment) and acupuncture versus sham needling (invasive treatment) are different from the previous three categories in that there is an intent to deceive subjects. The justification for the deception in the form of a placebo treatment is to control for 'expectations of benefit'. Again the issue of delay or denial of treatment is present.

In reviewing these five control options, two ethical issues become apparent. The first relates to the concept that acupuncture is still perceived as an experimental therapy and the second to the delay or denial of standard medical care. If we take the perspective that acupuncture is an experimental treatment then ethically we are required to ensure standard treatment, albeit an imperfect treatment, is not denied to the subject. This could be given at the completion of the trial (for the no treatment, the acupuncture versus biomedical care and the placebo and sham needling groups) or concurrently (for the acupuncture versus biomedical care group). Furthermore, it could be argued on ethical grounds

that the use of placebo or a no treatment control group is only ethical when there exists no effective treatment. The Declaration of Helsinki 3 is clear in enunciating this distinction:

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

In this day and age, very few diseases or illnesses do not receive at least partial benefit from standard care, therefore the use of placebo or a no treatment control could be considered as ethically dubious.

Conversely, it could also be argued that there is insufficient evidence if a placebo control is omitted from the trial. The omission could inhibit development and reduce therapeutic options.18 A recent study looked at the whether the outcomes of randomised control trials were influenced by the inclusion of a placebo group.19 A systematic review of nonsteroidal anti-inflammatory drug trials for arthritis treatment was done to evaluate the ratings of the efficacy of an active drug and the reporting of its adverse effects. They concluded, 'if efficacy is the outcome of interest, placebo control trials may be the most appropriate study design because patients participating in placebo drug trials are more conservative in rating a drug as being effective'. Although not directly applicable to acupuncture research, is does highlight the influence that the inclusion of a placebo control can have on the subject's belief and expectations concerning the efficacy of the treatment.

The second issue relates to impact that the delay or denial of treatment would have on the disease or illness being evaluated. Researchers are obliged to consider wheather the benefits, risks and burdens to the subject from delaying or denying treatment, outweigh the research objectives. The Declaration of Helsinki3 is again quite clear in expressing this view.

> Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others…

> Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits

If the disease to be treated in the trial was chronic and stable, the ethical considerations would be minimal. Control options would consist of no treatment, placebo controls or biomedical care models. As stated above, one strategy to ensure the subjects were not denied standard treatment, especially if the acupuncture was shown to be effective, is to offer the subject acupuncture treatment at the completion of the trial. This strategy again is acknowledged within the Declaration of Helsinki 3 which states that: 'at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study'.

If on the other hand, the disease was progressing quickly or had serious consequences if not treated immediately, then the only ethical option would be to use the acupuncture plus standard care versus standard care only model. The delay or denial of standard treatment has to be balanced against the possible outcome of the research and how the delay or denial will impact upon the subject's disease or illness. The principles of beneficence and maleficence have to be balanced against each other.

As has been demonstrated there is a close relationship between the choice of control, ethical issues and the need to develop a research design that is both rigorous and ethical. These three factors need to be considered early so as to develop a rigorous and ethical research model.

6. Informed consent

Obtaining informed consent from a subject prior to participating in a clinical trial is an important ethical requirement. The Declaration of Helsinki3 states that the researcher should fully inform the patient about aspects of care related to the research.

> each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing.

Informed consent safeguards the subject's 'right to be respected as a person and to have her personal goals and values given due weight by involving her in shared decision-making'.20 The inclusion of informed consent may however influence the result of a clinical trial by increasing the duration of a trial, modifying the characteristics of the population included in the trial (selection bias) and affecting the therapeutic response.21 A recent study investigated how the informed consent could be improved to reflect the patients' concerns and information needs improving enrolment and therefore minimising selection bias.22 They found that subjects often wanted information that was not ordinarily anticipated in the informed consent process. The additional use of information sheets, that incorporate specific information related to acupuncture, may well enhance subject recruitment by anticipating the concerns and information needs of potential subjects. Information such as attendance frequency, previous results from phase I or similar studies, specific side effects, contingency treatment plans and the offer of a debriefing after completion of the trial may facilitate recruitment.

7. Dissemination of results

Dissemination of research is often an overlooked ethical issue. Often clinical research that has had a negative outcome is not submitted for publication. In addition, journal editors may have a bias against publication of a negative outcome trial. Non reporting of negative trials should be seen as unethical and has been blamed for distorting the medical literature. Again the declaration of Helsinki3 is explicit in this regard stating that

> Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available.

Furthermore, acupuncture researchers may be reluctant to submit to a peer-reviewed journal because of the suggestion of reviewer bias concerning the publication of unconventional or alternative therapies. In a recent study Resch et al.23 demonstrated that there was reviewer bias concerning a fictitious but methodologically sound report on the effect of a homeopathic treatment for obesity. This is in contrast to an earlier similar study by the same research team where they found no such bias.24 Despite these equivocal outcomes and the possibility of rejection, researchers should be supported in their attempt to submit complementary and alternative medicine research for publication.

8. Conclusion

The consideration of ethics in the design and conduct of acupuncture clinical trials is fundamental to good research. Ethics must be seen as a tool that can be used flexibly. There are no definitive or final solutions to ethical issues. In fact, what the consideration of ethics does offer is a means to reflect on, and clarify issues and to see the issues in context of the research model. It is hoped that the discussion in this paper will generate more questions on the role of ethics in acupuncture research methodology.

Acknowledgements

I would like to thank Richard Hammerschlag PhD for his comments and editorial suggestions. Thanks also to Stephen Birch PhD and Mark Bovey MSc who organized the forum on acupuncture research at the University of Exeter, UK, at which this paper was first presented.

References

1. Daly J., McDonald I. Ethics, responsibility and health research. In: Daly J. (Ed.) Ethical intersections Health research, methods and researcher responsibility. Sydney: Allen and Unwin, 1996.
2. Campbell A., Charlesworth M., Gillett G., Jones G. Medical ethics. Auckland, New Zealand: Oxford University Press, 1997.
3. World Medical Association. International Declaration of Helsinki. <http//www.wma.net/e/policy/17-c_e.html>, Revised October 2000.
4. Unschuld P.U. Medicine in China – a history of ideas. Berkeley: University of California, 1985.
5. Humber J.M., Almeder R.F. Alternative medicine and ethics. Totowa, NJ: Humana Press, 1998.
6. Stone J. Ethical issues in complementary and alternative medicine. Complement Ther Med 2000;8:207–213.
7. Shapiro S., Louis T. Clinical trials. New York: Marcel Dekker, 1983.
8. Berman B.M., Swyers J.P. Establishing a research agenda for investigating alternative medical interventions for chronic pain. Complement Alternat Ther Primary Care 1997;24(4):74–758.
9. Edwards R.A. Research and the goal of improving patient care. Forsch Komplementarmed 1998;5(Suppl 1): 116–120.
10. Lao L., Ezzo J., Berman B.M., Hammerschlag R. Assessing clinical efficacy of acupuncture: considerations for designing future acupuncture trials. In: Stux G., Hammerschlag R. (Eds.) Clinical acupuncture Scientific basis. Berlin: Springer, 2001.
11. Jackson T. Health economics and policy: ethical dilemmas in the science of scarcity. In: Daly J. (Ed.) Ethical Intersections Health research: methods and researcher responsibility. Sydney, Australia: Allen and Unwin, 1996.
12. Larkins R. Basic research and the ethics of resource allocation. In: Daly J. (Ed.) Ethical intersections Health research: methods and researcher responsibility. Sydney, Australia: Allen and Unwin, 1996.
13. Caspi O., Millen C., Sechrest L. Integrity and research: introducing the concept of dual blindness. How blind are double-blind clinical trials in alternative medicine. J Alternat Complement Med 2000;6(6):493–498.
14. Cleophas T.J.M. Clinical trials: specific problems associated with the use of a placebo-control group. J Mol Med 1995;73:421–424.
15. Hammerschlag R. Methodological and ethical issues in clinical trials of acupuncture. J Alternat Complement Med 1998;4(2):159–171.
16. Vickers A.J., de Craen A.J.M. Why use placebos in clinical trials? A narrative review of the methodological literature. J Clin Epidemiol 2000;53:157–161.
17. Rothman K.J., Michels K.B. The continuing unethical use of placebo controls. The New England J Med 1994;331(6):394–398.
18. Kleijnen J. The use and abuse of placebo in clinical trials. Forsch Komplementarmed 1998;5(Suppl 1):125–127.
19. Rochon P.A., Binns M.A., Litner J.A. et al. Are randomised control trial outcomes influenced by the inclusion of a placebo group? A systematic review ofnonsteroidal antiinflammatory drug trials for arthritis treatment. J Clin Epidemiol 1999;52(2):113–122.
20. Faulder C. Whose body is it? The troubling issue of informed consent. London: Virago Press, 1985.
21. Dahan R., Caulin C., Figea L., Kanis J.A., Caulin F., Segrestaa J.M. Does informed consent influence therapeutic outcome? A clinical trial of the hypnotic activity of placebo in patients admitted to hospital. Br Med J 1986;293:363–364.
22. Casarett D., Karlawish J., Sankar P., Hirschman K.B., Asch D.A. Obtaining informed consent for clinical pain research: patients' concerns and information needs. Pain 2001;92:71–79.
23. Resch K.I., Ernst E., Garrow J. A randomized controlled study of reviewer bias against an unconventional therapy. J R Soc Med 2000;93(4):164–167.
24. Ernst E., Resch K.-L. Reviewer bias against the unconventional? A randomised double-blind study of peer review. Complement Ther Med 1999;7:19–23.