Limitazioni etiche negli studi di fase I

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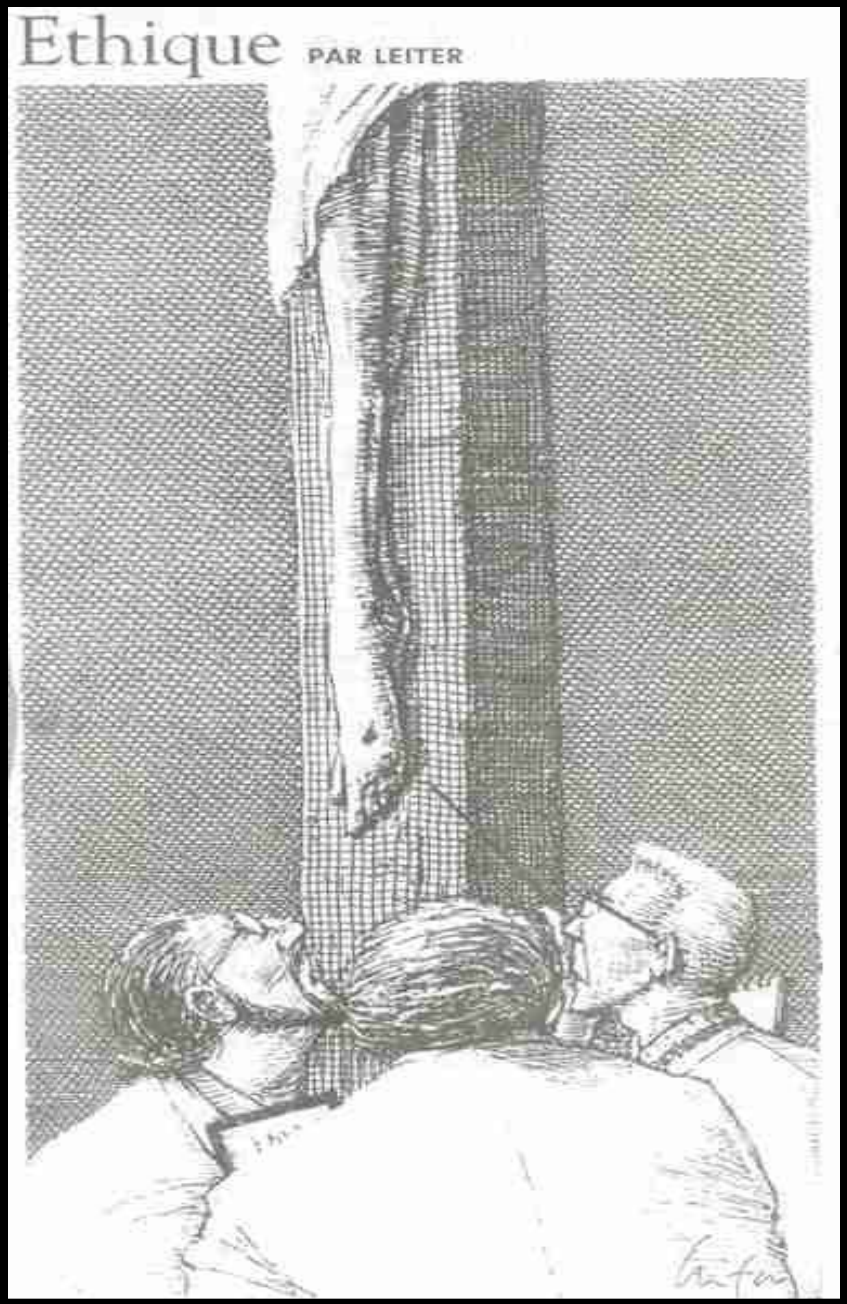
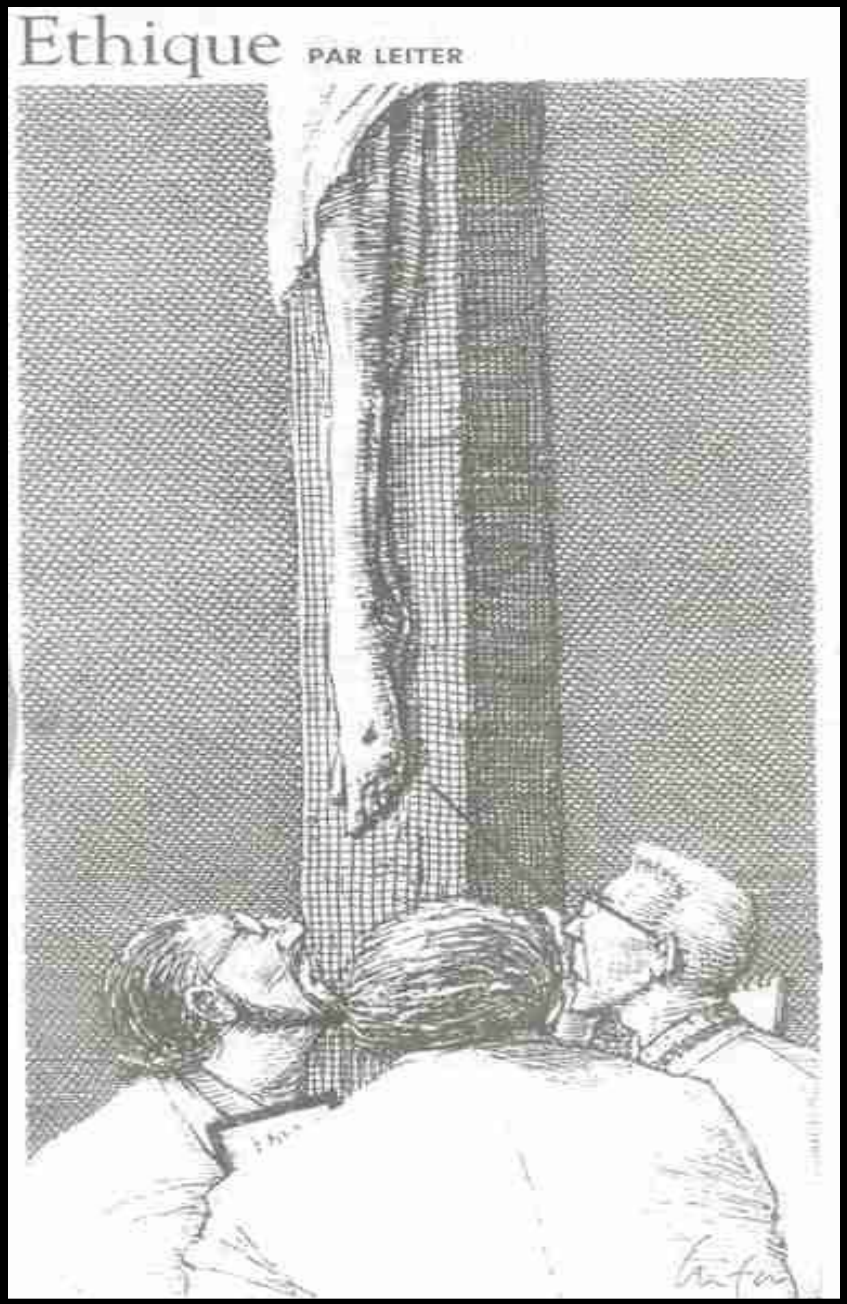
La farmacocinetica nello sviluppo del farmaco,
Facoltà di farmacia – dipartimento di scienze farmacologiche,

Milano, 5-6 febbraio 2009



Per chi si occupa di etica sono possibili almeno due approcci diversi



A) Affrontare la domanda centrale

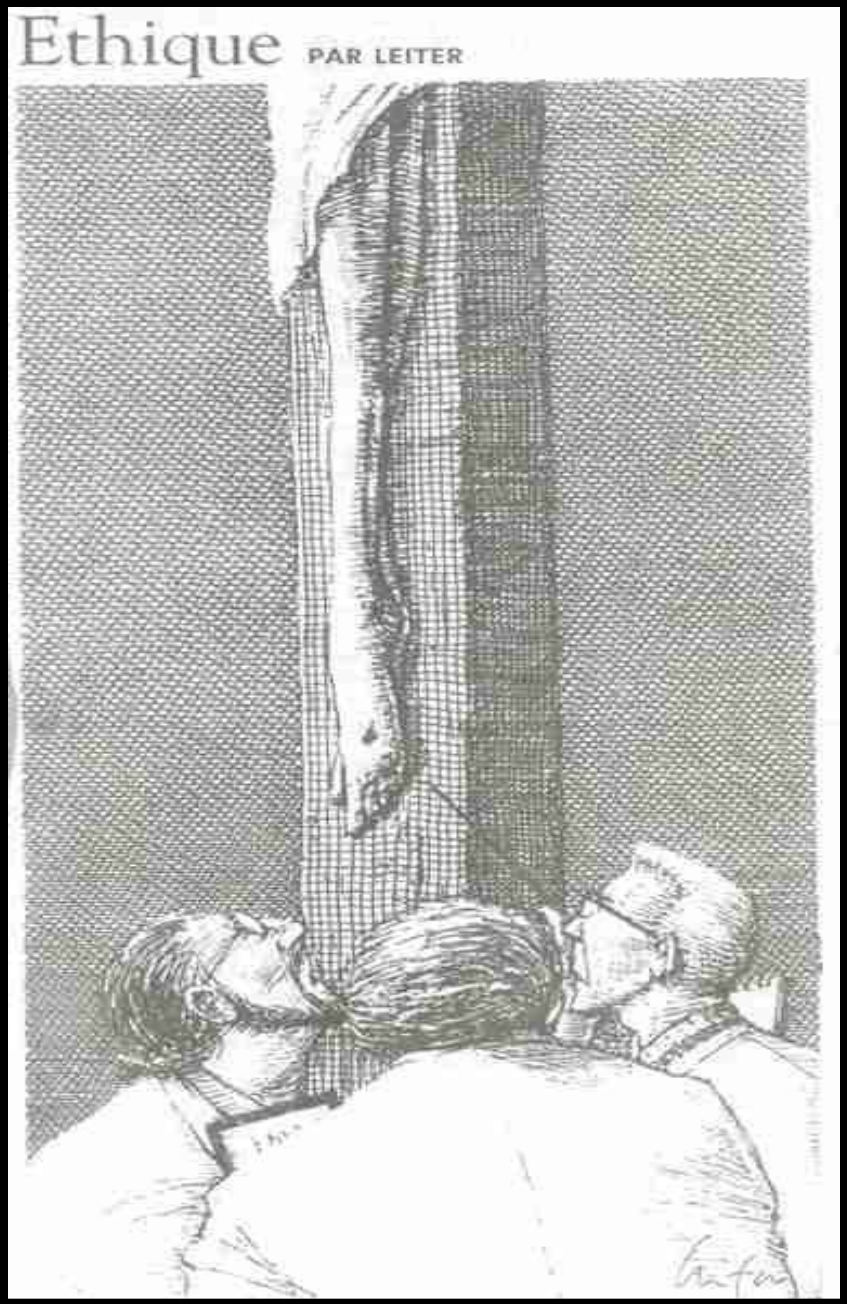
è lecito?

ne abbiamo il diritto?

Questa domanda non sembra tormentare troppo i filosofi ...

la sperimentazione sull'uomo è generalmente accettata – di più di quella sull'animale

"la sperimentazione sull'uomo è necessariamente immorale ma moralmente necessaria"

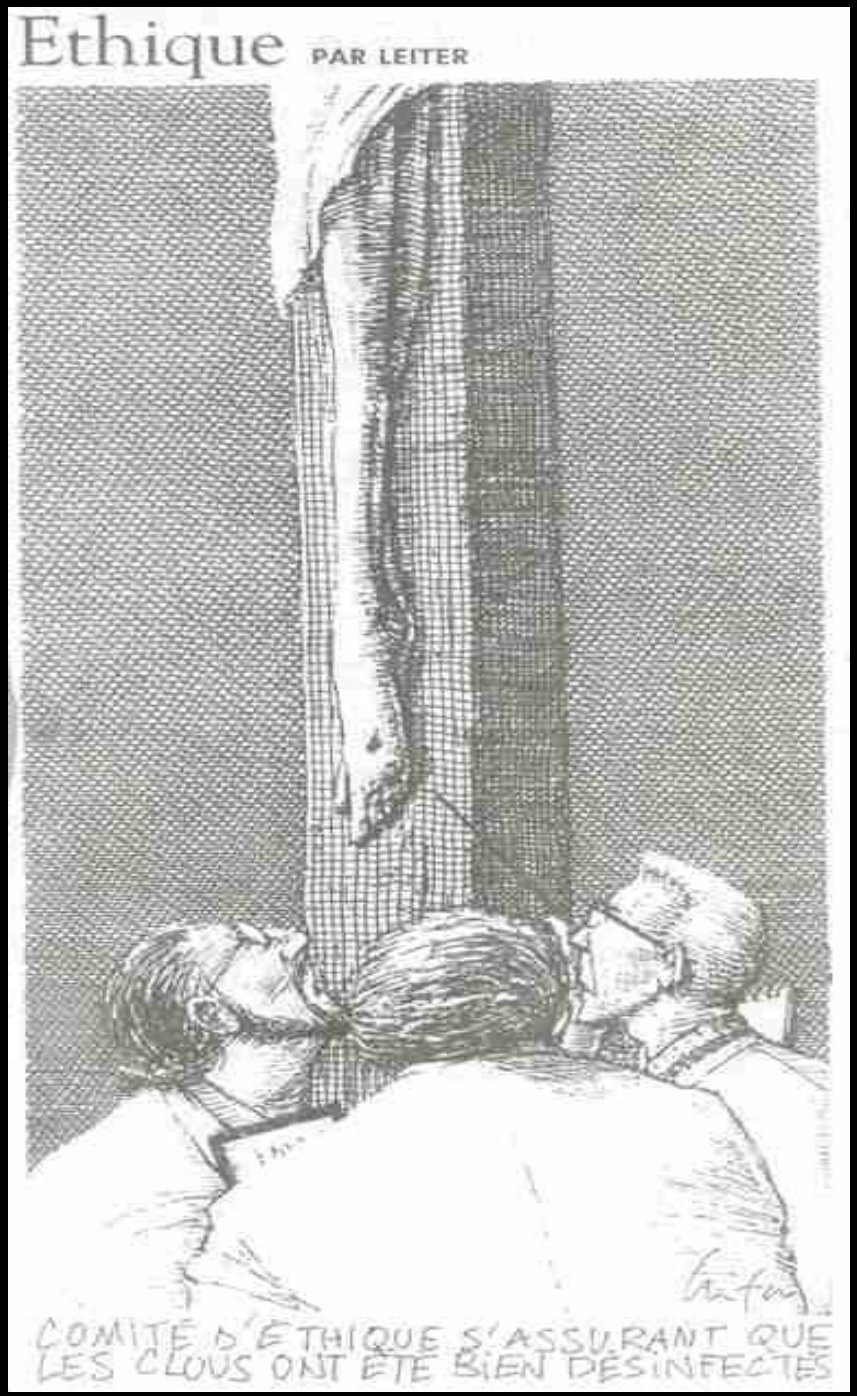


B) Stabilire delle condizioni minime

può essere fatto,

ma solo così

Per decidere se uno studio può essere approvato i Comitati Etici esaminano se queste condizioni sono rispettate



il comitato etico si sta accertando che i chiodi siano stati disinfettati bene ...

What Makes Clinical Research Ethical?

Ezekiel J. Emanuel, MD, PhD
David Wendler, PhD
Christine Grady, PhD

Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, we propose 7 requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies: (1) value—enhancements of health or knowledge must be derived from the research; (2) scientific validity—the research must be methodologically rigorous; (3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent—individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

JAMA. 2000;283:2701-2711

www.jama.com

WHAT MAKES RESEARCH involving human subjects ethical? Informed consent is the answer most US researchers, bioethicists, and institutional review board (IRB) members would probably offer. This response reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics.[1-4] While informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research.[5-8] Indeed, some of the most contentious contemporary ethical controversies in clinical research, such as clinical research in developing countries,[9-13] the use of placebos,[14-16] phase 1 research,[17-19] protection for communities,[20-24] and involvement of children,[25-29] raise questions not of informed

7 condizioni

- Valore della ricerca
- Validità scientifica
- Scelta dei soggetti
- Rapporto rischi / benefici
- Rispetto dei soggetti

sostanza

- Esame indipendente
- Consenso informato

forma

Studi di fase I – elementi critici

- Valore della ricerca
- Validità scientifica
- Scelta dei soggetti
- Rapporto rischi / benefici
- Rispetto dei soggetti
- Esame indipendente
- Consenso informato

Qualche considerazione

“ Une recherche n’est justifiée que si elle vise à générer de nouvelles connaissances scientifiques susceptibles de conduire à l’amélioration de la santé humaine. “

(Art. 5 Progetto di Protocollo aggiuntivo alla Convenzione europea sui diritti dell’uomo e la biomedicina concernente la ricerca nel campo biomedico)

Lo studio deve essere utile per la collettività

altrimenti si sprecano risorse limitate

le nuove molecole sono sempre un (reale) progresso?

“ i comitati etici rischiano oggi di fare la figura del palo della banda dell’Ortica, ovvero di chi guarda le pagliuzze e non vede la trave: che è oggi l’enorme questione morale di una ricerca che persegue oramai solo scopi di lucro.”

(Satolli, 2002)

le conoscenze generate devono essere messe a disposizione di tutti

è difficile approvare uno studio di fase I quando non si intravede nessun vantaggio almeno potenziale e un po' convincente della nuova molecola e quando si opera nella segretezza

It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

(Dichiarazione di Helsinki, art. 3)

In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

(Dichiarazione di Helsinki, art. 4)

Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

(Dichiarazione di Helsinki, art. 20)

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

(Dichiarazione di Helsinki, art. 21)

« Le rapport bénéfice/risque penche très nettement du côté du risque. Ces essais sont donc en contradiction avec la déclaration d'Helsinki à laquelle pourtant le rédacteur du protocole doit indiquer qu'il s'est conformé. »

(CCNE FR Avis N. 73)

L’intérêt et le bien de l’être humain qui participe à une recherche doivent prévaloir sur le seul intérêt de la société ou de la science.

La recherche ne doit pas présenter pour l’être humain de risque ou de contrainte disproportionnés par rapports à ses bénéfices potentiels.

(Protocollo aggiuntivo, art. 3 e 6)

È lecito usare volontari malati ?

Studi di fase I su malati

- Metanalisi in oncologia: ~ 5% risposta (0.3-0.7% completa) / ~ 0.5% morte tossica
- Influsso sulla qualità della vita / benefici non fisici

> Minimizzare la tossicità ma soprattutto tentare di massimizzare il beneficio !

È lecito usare volontari sani ?

Studi di fase I su volontari sani

- Per definizione beneficio = 0
- Rischio sempre > 0

C’è una via d’uscita ?

A) l’impiego di volontari sani è inevitabile, siccome imposto dalle normative internazionali.

Ma l’obbligo legale non è un argomento valido!

B) maggiore affidabilità scientifica dei risultati ottenuti.

“Human volunteer studies enable those responsible for the development of a new medicine to understand better the way it is absorbed and metabolised before beginning to study its clinical effect in patients.”

(ABPI, 1988)

C) l’impiego di volontari sani è giustificato da ragioni di sicurezza: un organismo sano offre maggiori garanzie di reagire positivamente in caso di effetti secondari dovuti al medicamento studiato.

E’ un sistema per minimizzare i rischi. Ma degli altri !

Studi di fase I su volontari sani

- Per definizione beneficio = 0
- Rischio sempre > 0

> Possibilità (contraria alla Dichiarazione di Helsinki ?) di considerare il beneficio per la collettività

> Obbligo di contenere i rischi

(come per la ricerca su incapaci di discernimento)

Condizioni supplementari per la ricerca senza beneficio potenziale diretto:

“ La recherche a pour objet de contribuer, par une amélioration significative de la connaissance scientifique, de maladie ou de troubles, à l’obtention, à terme, de résultats permettant un bénéfice pour la santé d’autres personnes et la recherche ne présente pour ceux ou celles qui y participent qu’un risque et une contrainte acceptables “ (Art. 8 pProtocollo aggiuntivo)

Fattori di rischio

- Passaggio animale - uomo
- Dose iniziale
- Grado di innovazione della molecola
- Incognite legate alla formulazione
- Ambiente di studio
- Fretta
- Incompetenza di chi decide ....

CORRIERE DELLA SERA.it

15 marzo 2006

Non è stato reso noto il nome della casa farmaceutica produttrice

Londra : sei gravi dopo test su farmaco

Gli uomini partecipavano dietro compenso a una sperimentazione per valutare la tossicitò della molecola

LONDRA - Due uomini versano in condizioni critiche e altri quattro sono gravi dopo aver partecipato a Londra ad un test clinico per la messa in commercio di un nuovo farmaco. Lo ha reso noto una fonte ospedaliera. I sei uomini, che erano stati pagati per sottoporsi ai test, sono tutti ricoverati nel reparto di terapia intensiva dell'ospedale londinese di Northwick Park, ha dichiarato un portavoce precisando che vi sono stati ammessi martedì sera a seguito di una reazione negativa al farmaco, un anti-infiammatorio per il trattamento, fra gli altri, della poliartrite reumatoide e della leucemia, L'Agenzia britannica per il regolamento dei farmaci e dei prodotti sanitari (Mhra), ha immediatamente ordinato la sospensione dei test, che venivano effettuati in una unità di ricerca indipendente dell'ospedale di Northwick Park, sotto la supervisione dell'americana Parexel International, un organismo che svolge le prove cliniche per conto dei laboratori farmaceutici.

It is also possible that this first trial in humans simply shows we are affected by the drug in a way that animals are not.

Taken together, these provisions make it very difficult to consider a Phase 1 trial ethical if it is not clear that there is a reliable technique for calculating a safe dose in that class of investigational medicinal product.

Theoretically, that could mean there might be certain types of product for which a regulatory requirement to conduct Phase 1 trials is inappropriate because it would be unethical to ask volunteers (healthy or not) to take such an unknown risk.

We have discussed in this report factors that should raise the level of caution for first human exposures to new agents. These include:

- any agent whose effects might cause severe physiological disturbance to vital body systems;
- agonistic or stimulatory actions;
- novel agents and novel mechanisms of action where there is no prior experience;
- species-specificity of an agent making pre-clinical risk-assessment in animal models difficult or impossible;
- the potency of an agent, eg compared with a natural ligand;
- multifunctional agents, eg bivalent antibodies, FcR binding domains;
- cell-associated targets;
- targets that by-pass normal control mechanisms;
- immune system targets;
- targets in systems with the potential for large biological amplification *in vivo*.

We have been assured repeatedly that proper procedures were followed, when the real question is whether they were the right procedures.

HEPATIC FAILURE AND LACTIC ACIDOSIS DUE TO FIALURIDINE (FIAU), AN INVESTIGATIONAL NUCLEOSIDE ANALOGUE FOR CHRONIC HEPATITIS B

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Abstract *Background.* We describe severe and unexpected multisystem toxicity that occurred during a study of the antiviral nucleoside analogue fialuridine (1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil, or FIAU) as therapy for chronic hepatitis B virus infection.

Methods. Fifteen patients with chronic hepatitis B were randomly assigned to receive fialuridine at a dose of either 0.10 or 0.25 mg per kilogram of body weight per day for 24 weeks and were monitored every 1 to 2 weeks by means of a physical examination, blood tests, and testing for hepatitis B virus markers.

Results. During the 13th week lactic acidosis and liver failure suddenly developed in one patient. The study was terminated on an emergency basis, and all treatment with fialuridine was discontinued. Seven patients were found to have severe hepatotoxicity, with progressive lactic acidosis, worsening jaundice, and deteriorating hepatic synthetic function despite the discontinuation of fialuridine. Three other patients had mild hepatotoxicity. Several patients also had pancreatitis, neuropathy, or myopathy. Of the seven patients with severe hepatotoxicity, five died and two survived after liver transplantation. Histologic analysis of liver tissue revealed marked accumulation of microvesicular and macrovesicular fat, with minimal necrosis of hepatocytes or architectural changes. Electron microscopy showed abnormal mitochondria and the accumulation of fat in hepatocytes.

Conclusions. In patients with chronic hepatitis B, treatment with fialuridine induced a severe toxic reaction characterized by hepatic failure, lactic acidosis, pancreatitis, neuropathy, and myopathy. This toxic reaction was probably caused by widespread mitochondrial damage and may occur infrequently with other nucleoside analogues. (N Engl J Med 1995;333:1099-105.)

It is not clear whether the problem is due to a manufacturing error, contamination or the wrong dosage.

Analysis of the infused TGN1412 has, to this point, indicated that it met the specifications of the manufacturer – that is, it was sterile and pyrogen-free and contained the expected amount of protein without contaminants.

Ethics committees considering first-in-man trials should have demonstrable access to acknowledge first-in-man experts.

It was considered that Ethics Committees should not be asked to adjudicate on matters that were outwith their remit or for which they are not equipped.

For first-in-man clinical trials of new agents that fall into the higher risk categories described in our remit, pre-submission meetings between sponsors and regulators, to identify potential concerns, would be useful to both parties, and are strongly recommended.

All six volunteers, who subsequently became patients, survived in part because of the extraordinary intensive are delivered during the critical stages of their illness.

In the UK, Ethics Committees decided if a site was suitable for a trial. When GCP inspectors inspected a clinical site it was to check for GCP compliance, not to authorise a site for a trial. The EMEA observer confirmed that this was the case in the rest of Europe.

We must do what we can to minimize risk, but the future health of the world population demands that we not let adverse events put an end to medical progress. We must treat those at risk with respect and great care, but the work must go on.

“Until now, such phase 1 trials have had a remarkably good safety record.”