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Causality Assessment of Adverse Effects

When Is Re-Challenge Ethically Acceptable?

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Abstract

One of the most difficult tasks in the evaluation of a medicine is whether it causes a particular rare and unusual (idiosyncratic) adverse effect. Such causality assessments are sometimes done by drug de-challenge and re-challenge. When the adverse effect is potentially serious, there is clearly an important decision to be made as to whether the re-challenge is justifiable and hence ethical. The recent controversy about the potential cardiotoxicity of fexofenadine, the fatalities associated with penicillin re-challenge and the fatalities associated with abacavir re-challenge highlight some of the potential serious risks of drug re-challenge. The associated important ethical issues are discussed. In particular, there is the need to ensure respect for the patient and to consider the scientific and social value of the re-challenge. A framework for evaluating and assessing the appropriateness of a particular drug re-challenge is proposed in the light of recent as well as long-standing discussions of drug re-challenge, patient informed consent and the ethics of human experimentation, in general. It is suggested that a drug re-challenge should be approached with the same rigour and standards of documentation as are currently required of clinical trials. Given the potential conflicts of interest inherent with any drug study, it is argued that the safeguards, as may be provided by scrutiny by an ethics committee, are necessary for a drug re-challenge. For the investigator contemplating the conduct of a drug re-challenge we would recommend the following: (i) a careful risk-benefit assessment as part of the decision-making process; (ii) careful scientific preparation, including appropriate expert support and emergency back-up facilities, if re-challenge is deemed necessary; (iii) the writing of a detailed protocol for independent approval and for safeguarding all concerned; and (iv) meticulous record keeping.

1. Causality Assessment

The identification and estimation of frequency of adverse drug reactions is an important aspect of the postmarketing validation of medicines.[1] One of the most difficult tasks in the assessment of such reactions is that of causality assessment. The gold standard for establishing cause and effect is de-challenge followed by re-challenge. Such a re-challenge is not without risk to the patient and therefore the question arises as to when such a re-challenge is ethical.

In a recent letter to the *Lancet*,[2] we questioned whether the re-challenge of a patient with fexofenadine, a histamine H_1 antagonist (antihistamine), was ethical.[3] We suggested that perhaps it was not because there are many other antihistamines available and the potential consequence of the re-challenge was quite severe. We were particularly concerned that, although on re-challenge QTc prolongation was observed, the investigators continued therapy until the patient developed polymorphic tachycardia, which necessitated defibrillation. Furthermore, terfenadine, the parent compound for fexofenadine, was known to induce QTc prolongation leading to ventricular fibrillation.[4] While volunteer studies suggested that fexofenadine does not prolong the QTc interval, it is well recognised that only extensive in-use experience can provide the necessary reassurance.[5] Clinical pharmacological studies are useful for validating new drugs and for providing first estimates of a drugs' safety.[6] However, such studies were insufficient for identifying the problems which subsequently surfaced with terfenadine. Increased attention was paid to the cardiotoxicity screening of fexofenadine. However, the clinical pharmacological screening, was likely to have been methodologically identical to that used for terfenadine, and necessarily limited in size. One would therefore expect the same inherent weaknesses, namely the exclusion of patients with concurrent disease, concomitant medication and genetic predisposition to particular adverse effects or interactions. Given that withdrawal of fexofenadine in the patient described by Pinto et al.,[3] led to normalisation of the prolonged QTc time and the previous history of cardiotoxicity of its parent compound terfenadine, a reasonable hypothesis might have been that fexofenadine was causally related. In our view, re-challenge of the patient with the drug exposed him unnecessarily to considerable risk, while alternative antihistamines that were likely to be better tolerated were readily available. In this case, we feel that the likelihood of harm overweighed the potential benefit. In answer,[7] the authors confirmed that patient consent was obtained as was required by Dutch law. They believed that their study was ethical since in their experience, fexofenadine was the only antihistamine which effectively relieved their patient's itch.

The case raises many issues, which we thought are worth revisiting, from a broader and more generic perspective.

2. The Potential Harm of Re-Challenge

The case presented by Pinto et al.[3] is not unique in illustrating the risks associated with re-challenge. The following recent cases and statistics are illustrative.

2.1 Re-challenging Patients who are Allergic to Penicillins with Cephalosporins

Anaphylactic reactions to antibacterials are still a problem and a recent study in the UK reported by Pumphrey and Davis[8] identified 67 cases of fatal anaphylactic reactions to drugs between 1992 and 1997. Of these, only 33 had been reported to the British Medicines Control Agency (MCA). 11 of the 67 cases had been attributed to antibacterials but only 4 of these 11 cases were on the database of the MCA, which also included a further case not previously registered.

Of the 12 fatal cases of anaphylaxis caused by ingestion of antibacterials, 6 were the result of exposure to a first dose of a cephalosporin.[8] Three of these 6 patients were known to be allergic to amoxicillin and 1 to penicillin. This would suggest that cross-sensitivity between the penicillins and the cephalosporins is much higher than is widely believed. Indeed, because of the close structural similarities between the penicillins and the cephalospo-

rins, we would expect a much higher cross-reactivity than the 10% rate, widely quoted.[9,10] Pumphrey and Davis[8] suggested that this might be due to the high false positive rate of allergies to penicillins. The high false-positive rate for penicillin allergy is borne out by a recent review.[11]

Oral or parenteral re-challenge of a patient with an allergy to a penicillin with the same or another penicillin is unjustifiable without skin testing.[11] For example, Pumphrey and Davis[8] recounted the case of a patient who developed a life-threatening reaction on re-challenge with amoxicillin. Two weeks earlier, she had to be resuscitated, following an anaphylactic reaction when given the first dose of a course of amoxicillin. It would appear that re-challenge with a cephalosporin is also ill-advised[9,10] without precautions applicable to re-challenge with a penicillin.

2.2 Ginkgo Biloba and Bleeding

Ginkgo biloba is a herbal product widely used for a range of conditions including memory loss and peripheral vascular disease.[12] Much of its use is without prescription. Therefore, reports of any potentially serious adverse effects raise substantial public health concerns. In a recent report, Vale[13] suggested that Ginkgo biloba use led to subarachnoid haemorrhage. The conclusion was supported by: (i) the observation that the patient had increased bleeding time, although neither the method used for measuring it nor the magnitude of change observed was given; (ii) the known activity of one of the ginkgolides, ginkgolide B, to inhibit platelet activating factor, which is essential for the induction of arachidonate-independent platelet aggregation; and (iii) reference to previous reports that ginkgolides or Ginkgo biloba extracts were associated with bleeding disorders. These included subdural haemorrhage[14,15] and spontaneous bleeding from the iris (hyphaema).[16] In the latter case, interpretation was complicated by the fact that the patient was also taking aspirin (acetylsalicylic acid). The bleeding stopped spontaneously and before the patient stopped taking the Ginkgo extract. Aspirin was continued without recurrence of bleeding over a 3-month period. A causal relationship therefore appears difficult to infer from this report[16] since bleeding stopped before the Ginkgo extract was stopped. Despite this, re-challenge would be unjustifiable, given the potentially serious consequences, although the debate will no doubt continue.[17,18]

Inference about whether there is any causal association between the bleeding disorders and Ginkgo would be made more robust by withdrawing the agent from patients already receiving Gingko and observing any changes in bleeding times. If bleeding times were to decrease, most observers would probably accept that there is a causal relationship between the observed episodes of abnormal bleeding and Ginkgo ingestion. A re-challenge to observe whether Ginkgo prolongs bleeding time in those who choose to resume Ginkgo consumption, despite warnings, would probably be viewed to be ethically acceptable by most people. However, the debatable value of the herb makes re-challenge difficult to justify in most circumstances.

2.3 Re-Challenge with Abacavir

Abacavir is a reverse transcriptase inhibitor, that has been recently approved for use throughout the European Community as part of combination antiretroviral therapy against HIV. Trial results, forming part of the registration dossier, showed that hypersensitivity reactions, manifesting as hypotension, fever, rash and multi-organ disturbance, occurred in about 3% of adult patients.[19] Fever and rash may be absent on re-challenge, thereby delaying and preventing the unmasking of otherwise severe hypersensitivity reactions. A diagnosis of drug hypersensitivity is complicated by the fact that the symptoms can mimic those of gastroenteritis, pneumonia, bronchitis, flu and pharyngitis. Further postmarketing experience of the use of abacavir, which has shown that such re-challenge can be fatal, has led to a redrafting of the Summary of Product Characteristics by the manufacturers and regulatory authorities. Specifically, the summary of product characteristics now states that the drug 'MUST NEVER be re-started in patients who have stopped therapy due to a hypersensitivity re-

action'.[19] However, this may provide insufficient clinical guidance unless the term 'hypersensitivity reaction' is well defined.

2.4 Re-Challenge with Tacrolimus

In a recent report on the association of concentric hypertrophic cardiomyopathy (CHC) with tacrolimus, 1 of the patients showed regression of the CHC on discontinuation of the drug.[20] However, the CHC recurred within 2 months of restarting the drug. A previous report had suggested that CHC was reversible on withdrawal of the drug.[21] Therefore, re-challenge was probably justifiable in this instance. There are few alternatives available and there is no guarantee that cyclosporin, for example, would be as effective in preventing organ rejection.[22]

3. Why Re-Challenge?

Drug re-challenge is undertaken for 3 main reasons: (i) to optimise the pharmacotherapy of the patient concerned; (ii) to guide oneself and others on the choice of therapy for future patients; and (iii) to generate new scientific knowledge.

Objective (i) focuses on the individual patient's perspective. In some circumstances there may not be an effective alternative. In most cases, by re-challenging one would be more confident about causality assignment and therefore make it less likely that the patient will experience continued exposure to a harmful drug, or deprivation of a useful but wrongly incriminated drug. Objectives (ii) and (iii) adopt a more societal perspective. The beneficiaries of the new-found knowledge in pursuing objectives (ii) and (iii) are society at large. All 3 objectives will, of course, serve the investigator well: good management of the particular and future patients, personal contribution to knowledge and personal research output and profile. The 3 objectives may at times be in conflict with each other. Trade-offs and objective criteria for deciding when re-challenge is justifiable are therefore necessary.

4. Criteria for Ethical Re-Challenge

Drug re-challenge must be viewed as any clinical research involving human participants is and as such it must adhere to the established ethical principles. In a recent, well thought out contribution, Emanuel et al.[23] suggested that there were 7 requirements for clinical research to be ethical. These are:

- social or scientific value
- scientific validity
- fair study participant selection
- favourable risk-benefit ratio
- independent review
- informed consent
- respect of potential and enrolled study participants.

Although the criteria set out by Emanuel et al.[23] are logical, it is obvious that each requires judgment. It is not immediately obvious how scientific value is to be traded against social value. What is a favourable risk-benefit ratio and what constitutes fair study participant selection? A study may be of great scientific validity but yet represent an abuse of the individual. The authors argued by reference to several sources that 'while informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research'.[23] Emanuel et al.[23] were well aware of some of the judgmental difficulties and illustrated application of their criteria with several examples. One involved trials of a rhesus rotavirus tetravalent vaccine. The vaccine was withdrawn from the US market because of postmarketing data that showed that the vaccine could cause intussusception in about 1 in 10 000 vaccine recipients. The authors suggested that while the risk-benefit ratio of the vaccine, which was associated with less than 5 in 1 million child deaths in the US, was not favourable in that country, this was not the case for developing countries. The trade-off was prevention of 1 death from rotavirus diarrhoea against 20 to 40 cases of intussusception in the US, compared with prevention of 50 deaths against 1 case of intussusception in developing countries. In their view, a trial in a developing country would be ethical provided there was informed consent, inde-

Table I. Criteria for ethical research involving drug re-challenge

Respect for the patient
Acceptable risk-benefit ratio: the drug must be substantially more effective than other alternatives and the condition being treated must be serious
Informed consent: the patient must be informed of the consequences of both the use of alternative treatments and the re-challenge
Scientific value
The re-challenge must be planned and recorded with sufficient detail so that inferences, which are as robust as possible, can be drawn
Social value
A significant number of future patients is likely to benefit from the drug and those at risk may not be easily identified to prevent them from being put at risk (e.g. patients with asthma)

pendent review and respect for enrolled participants. In this conclusion, they have assumed that the vaccine would be accessible (and affordable) to the developing countries and that the risk faced by the individual (intussusception) can be traded off against the benefit to society (deaths avoided). Neither assumption is as secure as it first appears to be as the current heated debate about access to medicines for the treatment of AIDS attest.[24] The balancing of societal and the individual participant's interests and the translation of theoretical benefits into tangible benefits (e.g. better risk-benefit for the citizens of the poorer countries given lack of access) are crucial aspects, which were perhaps inadequately addressed by the authors.

The trade-off between societal and individual utilities has particular relevance to drug re-challenge. We argued, in the case of fexofenadine,[2] that given the availability of effective alternative antihistamines, adoption of a societal perspective may provide some justification for the re-challenge. Our argument was that if the re-challenge provided more robust evidence for a cause and effect relationship, then fewer patients would in future be exposed to the drug and, hence, fewer patients would be harmed. Future benefits for the many would compensate for the potential harm to which the patient is exposed. Informed consent should, in such a case, make this clear to the patient.

5. Recommendations

The criteria put forward by Emanuel et al.[23] includes both judgmental aspects and control procedures. It may be useful to separate these 2 aspects and we attempt to do this in tables I and II. Informed consent is an important criterion for ethical research and signed informed consent ensures that the control procedures are in place. The apparent duplication is therefore meaningful. Moreover, some aspects discussed by Emanuel et al.[23] are nested within others. For example, respect for participants would require that the re-challenge has an acceptable risk-benefit ratio and that the participants are fully informed of the risks and benefits so that they can make their own judgments about whether to participate or not. We suggest that the criteria as set out in table I makes clearer the various possible distinctions and inter-relations.

To ensure that any re-challenge meets the criteria described in table I, we propose the safeguards shown in table II.

A possible protocol and 'aide memoire' for a drug re-challenge is shown in table III.

6. Conclusions

Research involving human participants raises important and specific ethical issues and decision making is often difficult. Given that the investigator is always faced with potential conflicts of interest, it is important that criteria are established on

Table II. Necessary safeguards for re-challenge

Prospective independent review of the need for re-challenge and the procedure to be adopted
Signed informed consent
Accurate and comprehensive records. These should include:
a good description of the 'initial' episode and the drug exposure
a detailed description of the adverse effects
the protocol used for the re-challenge. Any re-challenge must be managed by an expert. For example if cardiovascular complications are likely then a cardiologist should be present and emergency facilities such as resuscitation facilities should be made available. Monitoring must be designed in such a way that early signs of the relevant disorder arising from re-challenge can be detected
Regular independent audit of the records

Table III. Suggested protocol and 'aide memoire' for drug re-challenge

Making the decision (based on risk-benefit analysis)
Risk: re-challenge should be discouraged if:
– the anticipated adverse reaction is serious and potentially fatal
– the adverse event occurs rapidly and is difficult to prevent or treat
Benefit: the greater the benefit, the more worthwhile the re-challenge. The potential benefit would be greater if:
– the disease to be treated is
serious
common
– there are no or few other drugs for this disease, or they are less effective or more toxic than the drug to be re-challenged
– the potential adverse reaction is
serious
difficult to predict or anticipate
Scientific preparation for re-challenge
Questions to be addressed:
– have the biochemical/pharmacological actions of the drug and related compounds been fully investigated?
– have all the animal data been fully evaluated?
– has full advantage been taken of the possible use of surrogate markers to anticipate the adverse reaction, e.g:
a rise in eosinophils
histamine release
tachycardia
prolonged QT interval
Planning and re-challenge
Has a proper protocol been written?
Has it been reviewed by an ethics committee?
Will informed consent be obtained?
Will the patient sign a consent form?
Safeguards
Will the re-challenge be supervised by a suitable specialist best able to manage the anticipated adverse reaction?
Will there be appropriate:
– support staff?
– monitoring equipment?
– resuscitation equipment and drugs?
Documentation
The re-challenge should be performed as a serious, potentially dangerous scientific experiment. Therefore, it is important to:
– document the patients:
personal details
medical history
drug therapy
– and before and after the re-challenge:
all relevant physical signs
changes in laboratory parameters
electrocardiogram changes, etc.
Retain the relevant documents

which to judge the appropriateness of such research and interventions. When such criteria are set, it is important that appropriate systems are put in place to ensure that they are adhered to and interpreted consistently. We have made suggestions for the appropriate criteria to use and the control procedures that should be in place. The framework for classical clinical trials are reasonably well-established. Our reading of the literature suggests that in the area of drug re-challenge, a higher degree of formality may be necessary and we hope that this contribution initiates some further debate on the subject.

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