EDITORIAL

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Off-Label Pharmacovigilance

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This edition of *Drug Safety* contains the abstracts for the annual International Society of Pharmacovigilance (ISoP) meeting being held in Istanbul, Turkey, 26–28 October 2011.[1] Browsing the agenda for the meeting indicates that a session will be devoted to off-label use of drugs. This interesting topic has not been pursued much in pharmacovigilance, but it should be in the core of what we do.

In a recent editorial in *Nature Medicine*,[2] the risk of off-label use was exemplified by haemostatic agent recombinant factor VIIa (rFVIIa; also known as eptacog alfa) [NovoSeven®, Novo-Nordisk]. They referred to a postmarketing review of 35 studies showing increased risk of arterial thromboembolic events in patients with various clinical conditions, but not in healthy volunteers, treated with NovoSeven® through off-label use[3] as well as some other studies. Another review of rFVIIa concludes by saying "... The outcomes (effectiveness and safety) of all off-label uses should be systematically evaluated and reported. Adequate data to assess cost effectiveness for eptacog alfa does not exist for most off-label indications."[4]

The *Nature Medicine* review also points to an increase in off-label use of drugs in other therapeutic areas.

The US FDA has recently added a 'black-box' warning to NovoSeven®'s label of serious thrombotic adverse events linked to off-label use. These postmarketing findings have clear safety implications and the first, and obvious, message is that safety in conditions other than haemophilia could only have been signalled if the indication for using the drug was known. Individual case harm reports (ICHRs) often do not mention indication for use; moreover, during investigation of healthcare databases, I have found that it is not always clear what the indication for the use of a drug really is, and sometimes the labelled indication is mentioned when it does not seem correct for the clinical setting.

If we are to find early signals of this sort we must redouble our efforts to get full and accurate information both in ICHRs and also recorded in healthcare databases. Proven data quality is arguably a more pressing issue than 'underreporting'. The circumstances of off-label use of drugs certainly must be fully documented for there to be a chance of considering benefit or effectiveness to risk balance for the individuals treated.

Some years ago Kees van Grootheest and myself pointed out some approaches to tackle off-label prescribing.[5] In summary these were as follows:

1. Education: Clinicians need to know about the comparative merits of the effectiveness and risk of drugs, as well as how they work pharmacologically and toxicologically, and what interactions they have with each other.
2. Frequently, physicians do not consult the Summary of Product Characteristics (SPC) for verification, leaving aside whether they have taken notice of the contents of the official SPC in the first place. We recommended that the accessibility of SPCs should be enhanced for doctors and pharmacists, *drawing attention specifically to any changes*. There needs to be a single body of information that covers every drug.
3. Communication and understanding: There is much to be done in this area both in terms of follow-up and understanding of health professionals' behaviour and how to empower best practice. The dispensing pharmacist can play an important role in the implementation of warnings and contraindications.
4. Professional freedom: It goes without saying that doctors who issue off-label prescriptions

may need to justify their actions. Deviating from the SPC should always be a considered decision and health professionals need to be aware of the additional responsibilities associated with such a decision.

These proposals still apply today.

That the professional onus is very much on the off-label prescriber to make their experiences, good and bad, known should go without further remark. At the moment some will report successes with off-label use of drugs, but not the failures. Surely, this is another important role for pharmacovigilance since there is no other way for health professionals to report their experiences with drugs in a way that can provide a formal, efficient link to regulation, and might also lead expeditiously to the very necessary controlled trials to begin the process of objective effectiveness/risk analysis.

In talking to clinicians over the years, I have heard diametrically opposed views about off-label use. One physician expressed the view that competent physicians should fully understand the pharmacology and toxicology of drugs to the point where they could make decisions for use in their individual patients and that the labelled use was a kind of 'idiots guide' for the inexperienced. The opposite view was that prescribing off-label should be against the law or constitutes malpractice (in fact, many colleagues think this is so, which I suspect is why the stated indications in ICHRs and healthcare databases may be misleading in some cases). Neither of these extremes is correct and the *Nature Medicine* editorial recognizes this in giving an example of where off-label prescribing did lead to a new therapeutic development, even though the main message of the editorial concerned harm done.

1. A Personal Example of the Challenges

In the early 1970s I and another colleague, who later followed an eminent career in haematology, were keenly interested in the uses of fibrinolytic therapy, which was new then. We discussed its use in disseminated intravascular coagulation (DIC), also then a relatively unexplored condition. DIC leads both to a general microvascular thrombotic occlusion and at the same time to depletion of fibrinogen and platelets. The clinical result can be organ failure from thrombosis and bleeding in different degrees. At that time, and because our research interests were known, an 18-year-old post-partum woman was referred to us in extremis with phlegmasia caerulia dolens and DIC. One of her legs was massively swollen from the groin down and had frank gangrenous patches; the surgeon who was managing her at this time thought she would lose the leg to try to save her life, but in any case felt surgery would be very hazardous given the low platelet count. We jointly decided to try streptokinase fibrinolysis of the totally clotted leg, with informed consent from the patient, and ready availability of fibrinogen replacement. The result was successful, without any significant bleeding, and we reported the case.[6] By chance (given the relative rarity of this condition) we treated a second case with an equally good result.

Sometime later I treated two boys who had DIC following an attack of falciparum malaria. Both boys were unconscious and had peripheral cyanosis of their limbs which was well demarcated impending gangrene, and the attending physicians and surgeons considered that they would both probably die and certainly would lose hands and feet if they recovered. With parental consent I treated them with streptokinase with improvement after 24 hours, no significant bleeding and full recovery. These cases were also reported.[7]

Now I have done a literature search, which, although not extensive, has found a recent review paper from 2004 in which plasminogen activator has been used in several cases of DIC following meningitis.[8] The results are mixed, but particularly noteworthy is the high incidence of intracerebral bleeding. The authors propose that the treatment may be of value, although there are serious adverse effects, and rightly propose a multicentre controlled study. One question is of great interest here – was the bleeding specific to the underlying meningitis or is this likely to be as common in all uses of fibrinolysis for DIC? It is worthwhile noting that streptokinase is also fibrinogenolytic, and that plasminogen activator avoids this additional danger.

2. Conclusions

About 30 years have passed from the time of our early, successful off-label use of fibrinolytic therapy in DIC to now, and the scientific community is still considering the value of using such treatments in rare, dire, clinical situations. Would it not be much better, instead of relying on the uncertainties of reporting such clinical experiences in the literature, and even greater uncertainty whether they will be read, if we made the results of off-label use an essential part of pharmacovigilance? Can we not move to more rapid and rational evaluation of new treatments by reporting the results of off-label use, as part of pharmacovigilance, for regulatory and industry attention? The latter agencies can then expedite multicentre trials based on more solid hypotheses, as suggested.[4,8] Does it really need to take such a long time while we treat patients with continuing uncertainties?

A final, and very important point, is that much of paediatric prescribing is still off-label. I very much doubt that proposals for clinical trials in paediatric patients will be the full solution to rational therapy for all age groups of children. Surely we must, as a matter of priority, arrange for planned reporting of novel paediatric drug use experience as part of our various clinical and regulatory duties.

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