Editors' view

Drug code names and other ethics-related matters

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A rose by any other name . . .

'Rose is a rose is a rose is a rose.' Wikiquote (http://en.wikiquote.org/wiki/Gertrude_Stein accessed 7th January 2010) explains: 'The poem "Sacred Emily" by Gertrude Stein (1874–1946) is well-nigh impenetrable to the average reader but somehow it has managed to give a format phrase to the language. If something is incapable of explanation, one says, for example, "a cloud is a cloud is a cloud." What Stein wrote, however, is frequently misunderstood. She did not say "A rose is a rose is a rose," as she might well have done, but "Rose is a rose is a rose is a rose" (i.e. no indefinite article at the start and three not two repetitions.) The Rose in question was not a flower but an allusion to the English painter, Sir Francis Rose, "whom she and I regarded," wrote Constantine Fitzgibbon, 'as the peer of Matisse and Picasso, and whose paintings – or at least painting – hung in her Paris drawing-room while a Gauguin was relegated to the lavatory' (Nigel Rees, *Sayings of the Century*, London: Allen & Unwin, 1987). Sir Francis Rose was a friend of an aunt of one editor and would sign a note or invitation with a beautiful and stylized rose – his own witty take on the allusion. However, we at the BJCP have a less light-hearted attitude to naming (of drugs, at least). The relevant section of the instructions for authors reads: 'Drug names All drugs should be designated by an International Non-proprietary Name (recommended, rINN, or proposed, pINN). If such a name is not available, a drug should be designated by its British Approved Name (BAN; for example hyoscyamine) or its chemical name (for example glyceryl trinitrate). When a mixture of drugs has a combination BAN (for example cotrimoxazole, co-fluampicil), that should be used. For brevity, a company's code name may be used, but in that case the full chemical name or structure of the drug should be given in the introduction or a reference provided that gives this information.' The chemical name is usually a mouthful, and

a figure showing the structure often conveys the meaning more clearly – albeit less beautifully than Sir Francis's rose ideogram – but a reference to an accessible source (which may be a patent, where this provides the necessary information) will suffice.

We were recently disappointed to have to reject an interesting paper that had been favourably peer-reviewed because the authors, under pressure from the company that had sponsored the study, were not willing to provide the chemical name or structure of the drug they had investigated. The reason for the company's position was presumably commercial (they feared giving some hint to a competitor perhaps). The authors argued that the structure was of little interest to most readers and would become publicly accessible as the compound's development progressed. The editors discussed this view, but decided to stick to the Journal's policy, because if the compound did *not* progress the subsequent potential usefulness of the paper to the scientific community would depend largely on knowing the chemical identity of the drug.

An article in the current issue [1], supported by different companies, illustrates this concern. It describes pharmacodynamic (PD) properties of [27-0-3-{2-(3-carboxy-acryloylamino)-5-hydroxyphenyl}-acryloxy myricerone, sodium salt] a selective non-peptide ET_A receptor antagonist, aka 'S-0139' (less of a mouthful, if a bit dry and unrevealing). The authors provide a reference that identifies the chemical name (and hence structure) as well as the basic pharmacology of this drug, in their introduction (reference 5 in their paper). Why is this important? Sadly, the compound – intended initially for use in acute stroke – is not undergoing further development. So why would we publish a paper describing its pharmacodynamics? Precisely because other companies and investigators involved in drug discovery and development may learn useful lessons from the earlier experience. The paper addresses

one of the most crucial general issues of early-phase human studies, namely to help decide what dose and dosage regimen to use for subsequent definitive efficacy trials. In an ideal world such an investigation would focus on effects of the drug on ET_A responsiveness of the cerebral circulation, but it would be a foolhardy investigator who administered an ET_A agonist systemically at a dose that measurably altered cerebral blood flow. Instead, Martin Lunn and his colleagues determined the effects of S-0139, administered by intravenous infusion, on the vasoconstrictor response in the human forearm resistance vasculature to endothelin-1 (ET1) given directly into the brachial artery in a dose too low to cause systemic effects. Even in this peripheral vascular bed, ET1 infusion is not completely without risk of serious adverse effects: if the slow onset of action of ET1 is not appreciated, too rapid dose escalation could result in an acute compartment syndrome. Studies using ET agonists [2], including the present investigations, have therefore used constant rate, low dose ET agonist infusions that are relatively prolonged (90 min in the present investigations, compared with incremental dose steps of approximately 6 min for angiotensin). These are difficult studies to perform, with considerable demands on the subjects.

The paper describes three related studies – a pilot that established a dose range for S-0139, a formal dose response study (three doses versus placebo) and, the most interesting, a comparison of the effect of S-0139 on ET1 response during co-infusion versus ET1 response 3 h after stopping S-0139 (delayed). At the time of the delayed test dose of ET1 the measured plasma concentration of S-0139 (concomitant pharmacokinetic – PK – data) was an order of magnitude less than the lower limit of the pharmacologically active concentration determined previously in vitro. The extent of inhibition of the test dose of ET1 was indistinguishable between the co-administered and the delayed test dose. The explanation for this striking divergence between pharmacokinetics and pharmacodynamics is unknown, but must relate to the chemical structure of the antagonist. Possibilities include:

- a hit-and-run mechanism, either:
 - formation of a stable drug-ET_A receptor complex (slow dissociation, related chemically to bond type – as in covalent bonding between reactive grouping and receptor – or tight fit and corresponding van der Waal's forces, hydrogen bonding and other individually weak but cumulative forces), or
 - agonist-provoked receptor internalisation
- formation of a pharmacologically active metabolite of S-01039 in humans in vivo
- slow diffusion of S-1039 from the extracellular space bathing smooth muscle cells in the forearm resistance vessels that constitutes the biosphere accessible to the ET_A receptors (influenced by chemical structure of the

antagonist and its influence on endothelial transport or inter-endothelial cell diffusion)

- one or more of a number of other less direct mechanisms, for example relating to pre-equilibrium alterations in protein binding.

Awareness of this interesting biology should facilitate the development of chemically related ET antagonists, which will, one hopes, lead to therapeutic advances in stroke and other poorly met needs. If so, it will no doubt give satisfaction to the investigators of the present careful studies and to the volunteers who took part in these demanding and invasive experiments. We applaud the study's sponsors (*Shionogi-GlaxoSmithKline LLC*) for pursuing publication of work that may assist commercial competitors as well as (indirectly) future patients – one link between drug names and ethics, in case you wondered!

When is improvement not improvement?

Patient information (PIF) documents must be comprehensible if they are to perform their function and facilitate valid consent. Clinical investigators vary in their willingness and ability to write such documents effectively (not necessarily a swipe by an ageing editor at the ill-educated young: one suspects that a PIF written by Gertrude Stein might have taken some wrestling with). Furthermore, in studies that are commercially sponsored, company lawyers get in on the act; their interest is to protect the company and themselves, rather than to inform the potential volunteer. Literate lay and legal members of research ethics committees can help considerably, but may feel that it is a somewhat thankless task, and one that has the potential to slow down the approval process – itself an ethical issue [3, 4]. Consequently, there is unquestionably room for improvement. The Netherlands is in the forefront of encouraging brevity in PIFs (see www.ccmo.nl), specifying a maximum of 3 pages of A4 (1500 words) excluding the informed consent form, insurance text, rare side effects, and any general leaflet or flow charts that might be included. They emphasise that the starting point for a PIF must *not* be that the investigator seeks legal indemnity but that the PIF provides the study subject with the information he/she needs to take a well-considered decision about participation in the study. In this issue of the Journal, Adeline Paris and her colleagues describe a study [5] that investigated modifying an informed consent document either by a working group or by systematic improvement in its 'lexicosyntactical readability' (we think this phrase self-contradictorily means short words and good grammar). Regrettably, both methods failed. This is an important negative finding, not because it is sufficiently generalisable to close the issue (it does not, as the authors emphasise), but because it should stimulate further

systematic investigation in this important and under-researched applied field. Meanwhile, the finding should give pause to well-intentioned but time-consuming and research-delaying tinkering with such documents without deterring really important interventions. Professional members of research ethics committees, crucially including clinical pharmacologists, owe it to their fellow members to help sort the truly important from the trivial, so that when delays are occasioned they are in studies where misunderstanding the informed consent document will result in substantive failure of the validity of the consent process.

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