Editors' view

Looking back: editors' pick of 2008

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Negative studies

Editorial decisions are often considered to be a source of publication bias, simply because editors seem to favour manuscripts with positive or significant results. Critics of this approach argue (justifiably, in our view) that negative or non-significant findings in clinical pharmacology studies can be equally important to funding bodies, researchers and study participants, provided the study is sufficiently powered to exclude a biologically meaningful difference between active and comparator. (It is for this reason that we favour presenting the difference together with its 95% confidence interval for important negative findings.) A frustrated scientist once complained that he would spend months fruitlessly testing a particular molecule, only to discover, in a conversation with another group, that previous studies (unpublished) had been consistently negative. Why waste resources on further developing and experimenting with interventions where the available evidence indicates little prospect of clinical utility?

Looking back at 2008, BJCP has not shied away from publishing 'non-significant' but important studies. Take, for example, a randomized controlled trial of dexibuprofen in 255 children with upper respiratory tract infection [1]. Yoon and colleagues found no significant advantage in antipyretic efficacy or tolerability for dexibuprofen as compared to plain old ibuprofen, despite theoretical pharmacodynamic and pharmacokinetic reasons why the dexibuprofen enantiomer might be preferable. The findings of this study are consistent with trials of dexibuprofen in osteoarthritis which failed to demonstrate superior efficacy or safety over established analgesics. Is further research into dexibuprofen worth pursuing, or is it time to decide that 'as good as (but no better than) other analgesics' is simply not good enough for a crowded therapeutic arena?

Likewise, a systematic review reports little success in the hunt for genetic factors that might predict aspirin resistance [2]. Goodman and colleagues reviewed 31 studies covering 50 polymorphisms in 11 genes in 2834 subjects, and found only a heterogeneous and weak link between the PIA1/A2 variant and aspirin resistance in healthy sub-

jects. The potential association was not robust, as evidenced by considerable variation in the odds ratio (and statistical significance) arising from different laboratory assay methods, presence of cardiovascular disease, and choice of statistical model for the meta-analysis. Before going on to pursue polymorphism number 51, it would be better to standardize laboratory assays, exclude non-compliance with study protocols, and reach a consensus on the definition of aspirin resistance.

Non-significant results may be helpful in reassuring patients and medical practitioners in the field of drug safety. Grosso and colleagues applied an innovative technique, the self-controlled case-series, to investigate serious adverse reactions with strontium ranelate [3]. This novel approach uses patients as their own controls, comparing the relative incidence of particular adverse events within the specified post-exposure risk periods to other (control) time periods such as before or after drug exposure. While the self-controlled case series method was originally used to detect acute adverse events related to transient exposure (e.g. are children more likely to experience febrile convulsions in the 7–14 day period following vaccination, rather than at any other observed time period?) Grosso and colleagues have now usefully extended the technique to cover chronic therapy.

Negative pharmacokinetic findings can also be reassuring. Chloroquine remains a valuable antimalarial drug in many tropical countries despite increasing resistance. The WHO recommends chemoprophylaxis in those at high risk, including pregnant women. Given the potentially important role that desethylchloroquine might play in the efficacy and toxicity of chloroquine, it is surprising that few studies have been conducted on their placental transfer and infant exposure through breast milk. In a logistically challenging study, Law and colleagues studied such transfers in Melanesian women in a Health Centre on the north coast of Papua New Guinea [4]. They showed that cord to maternal plasma concentration ratios of both compounds were almost unity and that the relative infant dose via breast milk was about 3%. These essentially negative pharmacokinetic observations (no increased concentration in fetal compared with maternal plasma, a trivial dose to the suckling infant) support the safety of chloroquine when

used at the recommended dose in pregnant women and during breast feeding.

Biological macromolecules as therapeutic agents

The therapeutic drug class known as biological/macromolecule drugs has come of age and we are in an era of expanding biomolecular therapies targeted to bind to circulating and cell surface proteins, involved in the pathophysiology of a number of human diseases. The interferons (inferred initially from the phenomenon of viral 'interference') are among the most venerable of biological therapeutic drugs: they were discovered by Isaacs & Lindenmann at the National Institute for Medical Research at Mill Hill, London, in 1957 [5]. One can only speculate to what extent the ubiquitous tissue distribution and multiple subtypes of interferon receptors (I-1 α and II-1 γ) were an impediment to their clinical development. Friedman [6] comprehensively reviews their basic and clinical pharmacology, development and cautious clinical utilization as modern therapeutics. We are reminded that interferons have an established role in the treatment of the viral hepatitides (as mono or combination therapy for Hep. B or Hep. C, where pegylated interferons are preferred due to their long half-life), metastatic melanoma, metastatic renal cell carcinoma, multiple sclerosis and large life threatening haemangiomas.

Newsome and Ernstoff [7] provide an excellent overview of the nomenclature, origin, synthesis, clinical pharmacology, efficacy and toxicity of monoclonal antibodies (mabs) targeted at either cancer cell surface proteins or cells involved in the immune response or chaperoning cytotoxic agents to specific proteins on tumour cells. Presently, nine mabs are approved for the treatment of cancer in the clinic, variously targeting and blocking signaling at the epidermal growth factor receptor – EGFR (trastuzumab, cetuximab, panitumomab), CD20 (rituximab, ¹³¹I-tositumomab, ⁹⁰Y-ibritumomab tiuxetan) or CD52 (alemtuzumab). One of the most exciting novel monoclonal agents already in Phase I and II monotherapy and combination studies is the recombinant human protein apoptosis ligand 2/TNF-related apoptosis-inducing ligand (Apo2L/TRAIL) [8]. Apoptosis provides an important safety mechanism against neoplastic cell proliferation, however, some tumour cells develop specific mutations that enable them to escape apoptotic death. Apoptosis is initiated via two signaling pathways: one acting through the intracellular Bcl-2 protein family, the other through cell-surface pro-apoptotic (so called 'death') receptors. The development of pro-apoptotic agonists such as Apo2L/TRAIL may overcome cancer cells' resistance to apoptosis and thus condemn them to self-destruction in patients with leukemia, lymphoma, myeloma or solid tumors such as lung cancer [8].

In 2008 the *Journal* published reports on other therapeutic biologic macromolecules. Traczewski and Rudnicka [9] provide us with a comprehensive update on the systemic use of adalimumab, the first fully humanized anti-TNF α monoclonal approved for treatment of complicated and/or refractory psoriasis. This agent may in the future be used to treat other inflammatory conditions where TNF α is a primary mediator (e.g. rheumatoid arthritis, inflammatory bowel disease) and for which other anti-TNF α agents are already used clinically. In contrast, Costagliola et al [10] reported a prospective pilot study of intravitreally administered bevacizumab (a monoclonal which binds and inhibits both free and bound vascular endothelial growth factor [VEGF]) in patients with neovascular glaucoma, produced long lasting improvement in visual acuity and regression of iris neovascularization without toxicity for the 12 months of follow-up. Not surprisingly because of the intravitreal administration route in this prospective pilot study, no patients developed the rare reversible posterior leuko-encephalopathy syndrome associated with systemic bevacizumab therapy as reported by Burki et al [11]. Thus, during 2008 the *Journal* adequately portrayed the position that biological macromolecules are important target-specific cutting edge therapeutic agents.

Pharmacogenetics

Up to a third of type 2 diabetic patients do not respond to thiazolidinediones (aka 'glitazones'). By activating PPAR- γ , these drugs increase serum adiponectin, decrease blood sugar and improve insulin sensitivity. Sun and colleagues [12] assessed the impact of an exonic T45G single nucleotide polymorphism (SNP) and a promoter C-11377G on the biochemical response to rosiglitazone in Chinese type 2 diabetics. The promoter variant attenuated the effects of rosiglitazone on fasting plasma glucose, a model of insulin resistance and serum adiponectin whereas for the variant exon SNP, the serum adiponectin increase by rosiglitazone was enhanced. This study showed the role that pharmacogenetics can play in explaining the biochemical variability to rosiglitazone in Chinese diabetic patients and the important contribution of haplotype analysis.

Surrogate markers

Surrogate markers of drug action for diseases involving the central nervous system have been elusive but with advances in new technologies and techniques things are improving. In the brains of Alzheimer's disease patients, there is a deficit in cholinergic function, hence the therapeutic use of acetylcholinesterase inhibitors, albeit with low efficacy. Okamura and colleagues investigated acetylcholinesterase binding using [¹¹C]-donepezil and PET image analysis in two groups of Japanese patients of mild and

moderate disease severity, compared with elderly normal subjects [13]. Patients with moderate disease had about 25% reduction in binding throughout the brain, those with mild disease only in a few areas, suggesting a relationship between disease intensity and binding. Daily dosing with unlabelled drug resulted a 60% reduction in donepezil binding. This rather elegant study suggests that this PET technique could contribute usefully to investigation of the long term effect of cholinesterase inhibitors in Alzheimer disease, and that the technique could add to clinical evaluation in optimizing drug therapy for this debilitating disease.

Harmful effects of drugs and drug safety

The monitoring and analysis of adverse drugs reactions (ADRs) is a world-wide collaborative effort that is being boosted by data from rapidly developing and advancing countries such as India. In addition, some ADRs may be more prevalent in defined geographic regions due to distinct environmental and genetic factors that influence drug exposure and ADR susceptibility. Consequently, ADR epidemics will spread from such epicenters due to migration. Arulmani and colleagues working in a secondary care hospital conducted a prospective spontaneous reporting study over a 9 month period on inpatient admissions to medical wards [14]. It was co-ordinated by clinical pharmacists. The overall incidence of ADRs was almost 10% in 121 patients and included an almost equal mix of admission and hospital stay ADRs. Fortunately there were no deaths related to the ADRs. Antibiotics (our old favourites) contributed about a third of the ADRs and the average cost of management of the ADRs was 481 rupees (6 pounds). Such data are important as ADRs are of global concern.

Traditional observational studies still have a key role in pharmacovigilance. Diav-Citrin and colleagues prospectively collected data on a series of pregnant women exposed to paroxetine and fluoxetine, and found a significantly higher rate of cardiovascular anomalies in those taking fluoxetine as compared to unexposed controls [15]. While this is a signal that requires further investigation, it also demonstrates the fundamental importance of large scale databases in an era where collecting patient data is becoming increasingly hampered by bureaucratic hoops.

Another aspect of prescribing safety concerns the accuracy of the history obtained from patients. One day a computerised record system may exist in the UK which will improve access to this information. A paper from Denmark suggests that this is a worthwhile objective, easier to achieve perhaps in a relatively small country [16]. One interesting aspect of the medication history is the extensive use of over-the-counter herbal preparations, with potent pharmacological effects, such as St John's wort. Recovery to baseline from the enzyme inducing effects of

this 'herbal fluoxetine' can be quite prolonged [17]. It also draws attention to the importance of computerised prescribing in the general context of safety: certainly not a panacea but useful.

Patient focus

Patients often tell us, especially since the increased use of generic drugs, that they are able to detect differences between the effects of different brands of the same drug, even ostensibly of completely bioequivalent formulations. Usually prescribers reassure them that 'they are all the same'. They may be too optimistic. A paper in January [18] suggests that standard tests of bioequivalence may tell only part of the relevant story. Another paper in May reinforces this message for another class of drug [19]. Patients may indeed be right.

Therapeutics

Chronic obstructive pulmonary disease remains an intractable clinical problem and the introduction of phosphodiesterase 4 inhibitors is the first novel approach for many years. Drugs of this class are likely soon to be licensed for this indication [20].

Methods in clinical pharmacology

Where we did less well perhaps was in the field of methodology. In the beginning of the year we talked about the important role of clinical pharmacology as a supplier of tools and expertise in the growing field of translational medicine [21]. During the year we published only three papers about these tools, one about pulmonary function [22], one about a method for evaluating compliance [23] and one about measurement of cough [24]. We feel this is not enough for a specialist journal about a methodology intensive specialty. This year will be better with the start of our new branded methodology series [25, 26].

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