Editors' pick 2011

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Patient safety: dangers lurking in the background!

'Drug safety' is a major manuscript category that authors may opt for when submitting their papers to the British Journal of Clinical Pharmacology (BJCP). Indeed, papers submitted under many of the other manuscript categories such as 'Drug interactions', 'Pharmacogenetics' and 'Human toxicology' can also impact on the safety of medicines. Four publications in the Journal in 2011 highlight new and different aspects of drug-related safety under the themes of illicit drug substitution, drug-drug interaction assessment, tamoxifen pharmacogenetics in an Asian breast cancer population and comparative evaluation of criteria for assessing potentially inappropriate medication use in geriatric outpatients.

Over-the-counter, or more appropriately under-the-counter, slimming products often advertised and labelled as 'containing natural ingredients' are becoming more readily available especially via the internet [1]. Three clicks and it will be delivered to your door in 1 week! However, the products are unlikely to be effective and can be unsafe. Tang and colleagues [1] retrospectively reviewed poisoning cases involving illicit slimming products that were sent to their Princess Margaret Hospital Authority Toxicology Reference Laboratory (Hong Kong, China) for analysis. Over a 6 year period, 66 poisoning cases (one fatal and eight severe) were referred to them and in almost half the cases, patients' clinical presentations were consistent with the ingredients found. Examples included sibutramine and palpitations, fenfluramine and pulmonary hypertension. In addition, the medicinal chemists had been busy making analogues such as *N*-bisdesmethylsibutramine to try and fool the analytical chemists, unsuccessfully, in this case at least. One product contained six ingredients: sibutramine, fenfluramine, *N*-nitrosafenfluramine, phenolphthalein, anthraquinones and animal thyroid tissue! Such multi-ingredient combinations in a single illicit product appear to be an increasing trend, leading the authors to conclude

rightly that this could potentially lead to life-threatening drug-drug and herb-drug interactions. Buyer be very aware!

The plethora of drug-drug interactions continues to rise and in this field the Journal favours manuscripts that illuminate a new or relatively uncommon mechanism, whereas prescribers are concerned to avoid harm to their patients. However most decision-support tools include all published drug interactions irrespective of clinical applicability or appropriate pharmacokinetic analysis. Protein binding displacement interactions come to mind. Polasek and colleagues undertook a detailed and painstaking analysis of candidate inhibitors and inducers of the five most important drug metabolizing CYP enzymes [2]. They then obtained primary published literature on the candidate drugs and using four specific criteria, estimated the major perpetrators based on the FDA classification of strong, moderate and weak. Although they recognized several limitations to the analysis, such as excluding drugs not available in Australia or New Zealand, they catalogued and provided justification for accepting or rejecting each candidate as a major perpetrator. Ranitidine and raw palmetto (weak inhibitors of CYP2D6) were rejected based on level A evidence. There were 39 and 10 proven or likely major inhibitors and inducers, respectively. The analysis provides an evidence-based resource for prescribers, allowing for the safer use of some drugs which had been on the 'banned list'.

We now know that tamoxifen acts as an anti-oestrogen almost exclusively via its CYP2D6-mediated active metabolite, endoxifen. How many more drugs with CYP2D6-dependent activity are lurking out there that we do not know about? There is now a wealth of information demonstrating that CYP2D6 poor metabolizers have a higher risk of recurrent breast cancer when treated with tamoxifen, which has an overall failure rate of over 30%. The frequency of CYP2D6 poor metabolizers is substantially lower in the Asian population, but this population has a much higher frequency of the *10 allele which is

associated with reduced, but not absent, metabolic activity. In a comprehensive study in 165 breast cancer patients who were mainly Chinese with less than 10% Malay and Indian, Lim and colleagues showed that plasma endoxifen concentrations were on average 2.5-fold lower in homozygous **10/*10* carriers (whose concentrations approach those reported for Caucasian poor metabolizers) compared with heterozygous and homozygous wildtype carriers [3]. As the frequency of **10/*10* carriers is about 20% in Chinese and Malay subjects, but much lower in Indian subjects, the study highlighted the potential usefulness of pharmacogenetic testing in optimizing tamoxifen pharmacotherapy, making the drug more effective and safer.

The Journal receives many manuscripts in geriatric pharmacology, mainly drug utilization studies. We would also greatly welcome combined pharmacodynamic–pharmacokinetic studies in the very elderly, as this research area in people approaching their century is sorely lacking and drug safety is of particular concern in this age group, especially in individuals taking multiple medications. The term ‘polypharmacy’ is used but pharmacists can rightly retort that it is not dispensing pharmacists but prescribers who pump this medication pipeline. Many criteria have been published to assess potentially inappropriate medications (PIMs) based on ineffectiveness and/or high risk-benefit. Chang and colleagues assessed six published criteria that were developed in USA, Canada, France, Norway, Ireland and Thailand using a geriatric medication safety review study involving 193 elderly (≥ 65 , mean 76 years) adults [4]. They found that the proportion of patients who had at least one PIM ranged from 24% (Norway) to 73% (Thailand) and that the number of statements and availability of medications were the major determinants of PIM prevalence. This led the authors to conclude that criteria for the appropriateness of medication use may need to be country specific.

Prescribing matters and other pipe-dreams

One of the joys of reading the BJCP stems from the varied diet of articles, catering to a wide range of tastes, from the fastidious researcher to the eager (but slightly petrified) medical student. Here, an interesting and innovative proposal for a core drug list of 100 commonly-used or important drugs will surely be a great boon to students and educators who have been struggling with an ever-growing mountain of drugs [5]. The pains-taking endeavour of manually recording 7705 hospital prescriptions, plus the somewhat less onerous computerized analysis of 752 million primary prescriptions has helped to generate a list of drugs that new prescribers are most likely to run into from their first day at work. The core drug list will hopefully promote mastery of the common and useful, while shifting

the emphasis away from more esoteric agents that should really be left to specialist prescribers.

The strength of electronic prescribing databases is illustrated by another innovative study assessing the link between prescriptions of psychoactive drugs and road traffic accidents [6]. The investigators used a statistical method based on ‘probabilistic record linkage technology’ to connect the prescription database to police records of road accidents and driving licence data using items such as date of birth, initials and gender. Use of anxiolytics within the preceding week appeared to confer a greater risk of road traffic accidents, suggesting that the methodology is sensitive enough to detect an effect. Unexpectedly, use of selective serotonin re-uptake inhibitors (SSRIs) was also associated with increased risk of a road accident. In this complex area, novel approaches such as this can give us new leads, and prompt further work on possible effects of SSRIs on neuro-cognitive functions needed to drive safely.

Readers of the BJCP will of course recognize that not all intriguing hypotheses are subsequently confirmed when subjected to the acid test of the randomized controlled trial. In the light of empirical data indicating that smokers were less likely to experience post operative nausea and vomiting, Czarnetzki and colleagues set out to study the impact of nicotine skin patches on non-smokers who were undergoing surgical procedures [7]. Nicotine had no beneficial effect on post operative nausea and vomiting as compared with placebo, and worse still, patients treated with nicotine were significantly more likely to suffer from insomnia. This suggests that the postulated ability of smokers to resist post operative nausea and vomiting may stem not from acute pharmacological effects of nicotine but rather from other factors such as heightened tolerance to emetogenic mediators.

Views from the reviews

In the Reviews section of the *Journal*, particular highlights have been the publication of themed sections on ‘Drug allergy’ (in the May edition) and ‘Uro pharmacology’ (August) and one entire themed issue of the journal on ‘Haemostasis’ (October).

Drug allergy is an important clinical problem which can give rise to severe and sometimes life-threatening consequences. Confusion abounds as to what is a true allergic drug reaction and what is not. The articles in the ‘Drug allergy’ issue provided a comprehensive exploration of the nature of the phenomenon, its clinical consequences and the principles of management, as well as insight into the underlying immunological mechanisms – recognizing that not infrequently allergic reactions to drugs have more than one mechanism.

Functional disorders of the urogenital tract are common with increasing age and a cause of much distress especially in the elderly. They also have a major economic

impact in terms of healthcare and other resources consumed. The 'Uropharmacology' themed section dealt with the clinical pharmacology of drugs used to treat these disorders, principally benign prostatic hyperplasia and overactive bladder. A major theme of this section was to highlight the particular need for safety and selectivity in the treatment of such conditions, due to the higher propensity for adverse effects in the elderly as well as the fact that the disorders being treated are not in themselves life-threatening. This is clearly an area which has been relatively neglected, having been historically the province of surgery, and where more research into novel therapeutic targets is sorely needed.

The 'Haemostasis' theme was an especially noteworthy highlight. This was an encyclopaedic tour of current issues surrounding the use of anti-platelet and anticoagulant medications. This was particularly timely, given the very topical interest in novel anti-platelets and anticoagulants. Ticagrelor is a potent and reversible P2Y₁₂ antagonist, the prototype of several more such drugs in the development pipeline, which has recently been licensed for the treatment of acute coronary syndrome. Indeed, NICE have recently approved its use in this condition. This and related drugs are set to revolutionize the treatment not just of acute coronary syndrome but also of other arterial thrombotic diseases, and this will be the subject of much clinical research in the near future. The novel direct thrombin and factor Xa inhibitors have also created much news in recent times, particularly in respect of their place in the prevention and treatment of thromboembolic disease including atrial fibrillation, deep vein thrombosis and pulmonary embolism. In atrial fibrillation, in particular, dabigatran, rivaroxaban and apixaban have shown great promise in recent trials, demonstrating non-inferiority (and in some aspects potential superiority) over warfarin, so that we now have available anticoagulant drugs with relatively wide therapeutic indices which do not need routine monitoring. This has the potential to change radically the landscape in anticoagulant therapy, although it also seems clear that we are a long way yet from seeing the demise of warfarin. These and other issues were explored in depth in this issue.

'Juices! which juice or no juice, that is the question?'

Clinical pharmacologists are at the leading edge of defining and understanding the complex relationship between diet (food and drink) and drug disposition, specifically the growing scientific understanding of fruit juice–drug interactions. Naturally occurring furanocoumarin derivatives contained in grapefruit juice (e.g. 6'-7' dihydroxybergamottin) down regulate expression of and directly inhibit CYP3A enzymes, especially in enterocytes in the small bowel [8–10]. Hepatocyte CYP3A function is affected only

at higher quantities of grapefruit juice ingestion. Grapefruit juice also inhibits the drug efflux transporter ABCB1 (MDR1; P-gp) found on the luminal membrane of enterocytes and the bile canalicular membrane of hepatocytes, due to its content of the flavonoid, naringin [11]. Furthermore naringin also inhibits the uptake (influx) organic anion transporting polypeptide 1A2 (OATP1A2 also known as SLCO1A2) found in the duodenal enterocyte and the cholangiocyte and possibly also inhibits other solute carriers of the OATP (SLCO) family [11].

During 2011 the Journal published a study by Reddy *et al.* [12] which investigated patients treated chronically with atorvastatin at a stable dose of 10, 20 or 40 mg day⁻¹ who ingested 300 ml day⁻¹ of Florida grapefruit juice for 90 days. One cohort (arm A, *n* = 60) continued with their current dose of atorvastatin while the second cohort (arm B, *n* = 70) halved their atorvastatin dose. Serum atorvastatin, lipid profile, hepatic function and creatine phosphokinase were measured at baseline and at 30, 60 and 90 days after initiating grapefruit juice. In arm A patients, consumption of grapefruit juice increased serum atorvastatin exposure by 19–26% compared with baseline, but had neither a clinically significant effect on the lipid profile nor did it cause detectable adverse effects on hepatic or muscle enzymes. In arm B patients a 15–25% reduction in atorvastatin exposure was accompanied by significant elevations in serum lipids. The study provides important clinical data that the interaction between grapefruit juice and atorvastatin does not require atorvastatin dose reduction, and additionally does not lead to increased adverse drug effects, at least over a 90 day period. These results, in patients, challenge the extrapolation of data from earlier studies where 'larger' doses of grapefruit juice were studied in volunteers with results that suggested an extensive juice–atorvastatin interaction [13], but are in keeping with investigations where more moderate ingestions of grapefruit juice were studied [14].

An e-publication of a case report in the Journal [15] described a 52-year-old Caucasian woman with advanced unresectable oesophageal squamous carcinoma who had progressed through several combinations of chemotherapy treatment and was being treated with intravenous docetaxel (40 mg m⁻²; = 74 mg), gemcitabine (800 mg m⁻²) and daunorubicin (30 mg m⁻²) administered on a single treatment occasion every 2 weeks. She was undergoing 'therapeutic monitoring' for docetaxel. Analysis of the docetaxel concentration vs. time data using NONMEM yielded a docetaxel clearance of 13.2 l h⁻¹ (AUC 5.61 mg ml⁻¹ h). She was not concomitantly taking any drugs that would inhibit CYP3A, but reported drinking one glass a grapefruit juice (approximately 250 ml) daily for 3 months. She stopped ingesting grapefruit juice for the next treatment cycle, when her measured docetaxel clearance increased to 34.1 l h⁻¹ (AUC 2.17 mg ml⁻¹ h). These pharmacokinetic data were accompanied by docetaxel pharmacodynamic effects on neutrophil counts. The pharmacokinetic effects

could potentially be explained by the furanocoumarins in grapefruit juice reducing hepatic CYP3A function and thus docetaxel clearance. But in addition the possible effect of the naringin in grapefruit juice inhibiting ABCB1-mediated efflux of docetaxel into the intestine and bile must also be considered [16]. This intriguing case report suggests the possibility of a significant grapefruit juice–docetaxel pharmacokinetic interaction of similar magnitude to that caused by established inhibitors of docetaxel metabolism and requires confirmation in a larger controlled clinical investigation.

An interesting variation on the grapefruit juice theme in the Journal was the study by Taipinen *et al.* [17], which described the effects of apple and orange fruit juice on aliskiren pharmacokinetics and pharmacodynamics. This was a randomized three-way crossover study in healthy volunteers ($n = 12$), who ingested 200 ml of orange juice, apple juice or water three times daily for 5 days. On day 3, they ingested a single 150 mg dose of aliskiren. Plasma aliskiren concentrations were measured up to 72 h, its excretion into urine up to 12 h and plasma renin activity up to 24 h after dosing. Orange and apple juice significantly reduced both $C_{\max}$ (of aliskiren) by 80% and 84% respectively and AUC by 62% and 63% respectively. Importantly the juices had no significant effect on aliskiren elimination half-life or renal clearance. Plasma renin activity mirrored the pharmacokinetics and was 87% and 67% higher at 24 h after aliskiren during the orange juice and apple juice phases, respectively, than during the water phase ($P < 0.05$). The postulated mechanism underlying these findings is that flavonoids (e.g. hesperidin) present in apple and orange juices inhibit aliskiren uptake into the enterocyte. This is mediated by the drug influx organic anion transporting polypeptide 2B1 – OATP2B1 (SLCO2B1) [11, 18]. The data from this study support the position that concomitant intake of either of these juices with aliskiren is best avoided.

These publications in the Journal during 2011 emphasize the complex effects of fruit juices on concomitant drug therapy mediated by variable and often profound modulation of drug metabolizing enzymes and influx and efflux drug transporters in the enterocyte, hepatocyte and biliary tree. The astute clinician/clinical pharmacologist should always be probing their patients' 'environments' for clues to better understand instances of drug toxicity or therapeutic failure.

Littluns (and less than littluns . . .)

We have commented before on paediatric clinical pharmacology [19]. There is still an enormous shortage of knowledge about pharmacokinetics and dynamics in children, as well as clinical effects of drug treatment on issues of special importance for this age group, including growth and learning performance. The schemes that have been

instituted by regulatory agencies to stimulate research with new medicines in children have yielded a considerable and even frightening backlog of so-called Paediatric Investigative Plans (PIPs). How all these studies (currently between 500 and 1000) can be done in a vulnerable population that rightly gets enhanced ethical and regulatory protection is difficult to envisage. Clinical pharmacology has something to add here, as innovative study design, data analysis and modelling can each play a role in producing small but valid studies that can still hit the spot.

It is gratifying that we see a steady increase in the number of submissions describing research in children and this year we published a bumper crop of 16 papers. Not all are experimental, and some of our authors have investigated patterns of drug use or other pharmacoepidemiological data. Lindkvist *et al.*, for instance, studied off label use of triptans in Finnish children [20] and Neubert *et al.* studied geographic variation in prescribing of anti-diabetic agents in Europe [21]. Mahmood investigated the predictive power of a model for morphine clearance as a function of age [22]. Population kinetics (with sparse sampling) is well suited to obtaining useful pharmacokinetic information from clinical cohorts, as exemplified in a paper by Foissac *et al.* on anti HIV agents [23]. Developmental age affects drug metabolizing capacity and also the toxicity of drugs like mercaptopurine, which was studied by Adam de Beaumais *et al.* [24] in children with leukemia and by Yanagimachi *et al.* in juvenile idiopathic arthritis [25]. While children are not small adults, sadly they are not untouched by the obesity epidemic and there is an increasingly population of big children, in the wrong dimension. Chiney *et al.* studied xanthine oxidase activity in a group of obese children [26].

Looking at this collection of papers we are excited to see that our authors are meeting the challenge of the knowledge gap in paediatrics, but the size of this gap remains awesome and we are only scratching the surface of the body of questions remaining. So we will encourage the submission of more papers in this area strongly in the years to come.

Competing Interests

There are no competing interests to declare.

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