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Commentary

Personalised medicines: More tailored drugs, more tailored delivery

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1. Introduction

While more knowledge of the patient genome will undoubtedly bring many benefits for patients, this by itself is unlikely to correct the shortfalls in current medication prescribing, usage and monitoring (pharmacotherapy). Special efforts are necessary to ensure that the medication process is improved so that avoidable problems do not diminish the scientific and technical advances in therapy which would otherwise be brought about. Genomics have the power to improve the target selectivity of drugs, the selection of volunteers and patients for clinical trials and hence the chance for success of many agents in specific populations and individuals, which is the key promise of personalised medicine. Personalised medicine has to be linked with personalised *medicines* and their personalised *administration*. Hence the title of this commentary uses the word "delivery" in its two senses: first, the traditional sense of optimization of drug delivery via formulations and devices; and second, the physical delivery and administration to/by the patient. Personalised medicine involves the correct diagnosis, the correct choice of drug, the choice of optimal dose, the calculation of the dose for specific individuals and drug administration at the appropriate *time* and, as with intravenous medication and implanted pumps, the proper *rate*.

2. More than the drug

As can be appreciated, the drug substance although a key part of therapy is not the only factor in achieving successful outcomes. If there have been strategic mistakes in approaches to drug design in the last decade, it has been that molecular biological and informatics experts as well as high through-put screening advocates have perhaps sometimes minimised the fact that a drug and its target are not close neighbours *in vivo* (as opposed to *in silico*) unless the drug can reach the required sites in sufficient quantities, without degradation into inactive or toxic metabolites, or sequestration by unwanted sites. This is obvious, and has been for a long time, but the "druggability" of putative therapeutic agents has often been wanting. There is an additional but crucially important fact: if patients do not take their medicines, then the there is no action, no benefit, and of course potential harm. Indeed, improving patient adherence to prescribed treatment regimens remains a formidable challenge to be overcome.

3. An elusive goal

Biotechnology is leading the way in transforming the landscape of medicine and the pharmaceutical industry. Twenty-five years since the introduction of recombinant human insulin, biotechnology has gained momentum in driving innovations in therapeutics. Regenerative medicine and genetic medicine are two such examples at the forefront of biotechnology. Biotechnology is not only a source of new medicine, but is also a driver for revolutionizing drug development. Today, medicinal chemists are in a better position to maximize the return on investment because of the improved understanding of disease at the molecular and cellular levels. Advances in biotechnology, nanotechnology, and information technology are helping patients to benefit from tailor made therapeutic intervention. The judicious application of the products of biotechnology will lower health care cost in the long run and increase productivity in the private sector. But personalised drug therapy has long been an elusive goal in therapeutics. The main reasons for this paradox are lack of the requisite tools, lack of incentives, economic barriers and perhaps even medical and pharmaceutical professional inertia.

4. Multiple influences

The complex of influences on personalised medicines is summarised in Fig. 1 (Lee, 2010). Clearly there are many, sometimes competing, pressures.

Although just about all drug candidates are evaluated in subjects with one disease under well controlled clinical trial conditions, patients with a chronic disease are more apt to suffer from one or more other chronic diseases. A strong case can therefore be made for designing ways to offer flexible drug delivery profiles to accommodate disease–disease interaction in addition to minimizing drug–drug interactions. Patients 65 years old or beyond may be prescribed an average of 13 drugs and as many as 28. The challenge, therefore, is to devise delivery systems that can allow the *de novo* assembly of multiple medications immediately prior to use. This

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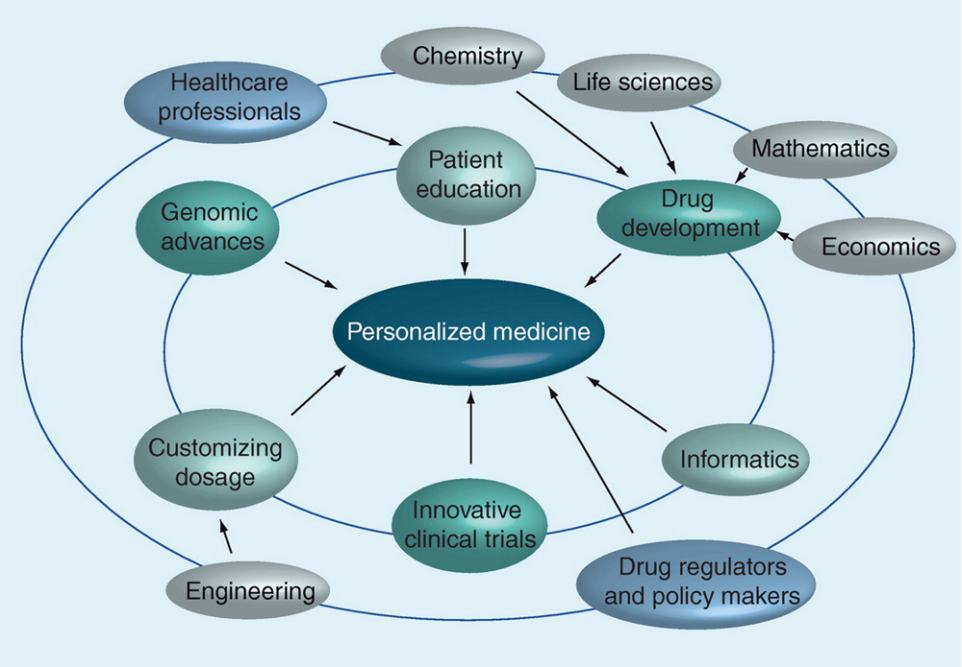

Fig. 1. Factors, scientific, economic and professional, impinging on the development and potential of personalised medicine, from Lee (2010).

task may be facilitated by increasing the potency of the drug itself, and advances in technology.

5. Adverse events and problems of compliance: the iceberg factor

While adverse events and failure of compliance are important and have been studied widely, they often have not been addressed with a view to finding technical solutions. Adverse events due to prescribed medicines in elderly patients leads to an estimated 15–20% of hospital admissions (Chan et al., 2001). The financial cost is enormous; worse, there are reckoned by some sources to be some 80,000 deaths per annum in the USA and 8000 per annum in the UK attributed in one way or another to prescribed drugs. Official figures might assert otherwise, in part due to the massive under-reporting of adverse reactions and morbidity due to the use of prescribed medicines (see e.g. Hazel and Shakir, 2006). This leads to what we can call the "iceberg effect." The UK MHRA revealed close to 1000 patients died in 2006; Phillips et al. (1998) reported figures from the USA, now more than a decade old: 7391 deaths due to medication errors. These figures are much less than the estimated numbers. Much depends on the definitions of error. Whatever the true numbers, there are clear signs that the numbers are increasing (Ferrer and Anron, 1998) and no sign that reporting is increasing.

Fig. 2 attempts to summarise the gap between theoretical and actual outcomes due to multiple failures often in secondary care institutions which have all the expertise to avoid such events.

The failings of present-day therapy as shown in Fig. 2 include what appear to be trivial problems, but all of these mistakes of administration (not to mention prescription errors and erroneous dose calculations with parenteral and paediatric medicines) are recorded in the literature. Patient compliance, a phenomenon sometimes aligned with the patients' experience of the therapy (suffered side effects, bad taste for infants *inter alia*) as well as other personal and psychological factors. A drug not taken, or taken at the wrong intervals, in under-dose or over-dose defeats its design parameters; hidden non-compliance can lead to poly-pharmacy and the prescribing of inappropriate alternatives to the originally prescribed drug which apparently has not worked.

Medication adherence is seen to be a priority in health care reform (Cutler and Everett, 2010). Past experience shows that it cannot be assumed because drugs are either critical for a patients survival and selected with care, that compliance is automatically high. Patients on immuno-suppressive drugs are sometimes poor adherers (Chisholm et al., 2005). In some cases, as many as 67% were non-adherent, and three quarters of these had sub-target drug plasma levels.

Medication error is by no means a new issue. Close to half a century ago, Fogg (1965) discussed errors in UK hospitals and Vere (1965) highlighted a contributing factor, errors of complex prescribing. A paper 22 years ago (Raju et al., 1989) discusses such issues in one of the most vulnerable groups and critical areas of medicine—paediatric intensive care. Aspects of paediatric medication are discussed by Knibbe and colleagues in this issue (Knibbe and Danhof, 2011). Not for nothing has this varied patient group been described as neglected (Florence, 2008). Fig. 3 summarises some of the other issues which contradicts the concept of the simplicity of medication. If present practices are allowed to continue this will totally defeat the object of personalised medicine.

6. Professional cooperation: medicine and pharmacy

Clinicians themselves have sometimes admitted (Biesecker, 2009) to being "inefficient at prescribing, monitoring and using the optimal drug for each patient." Although most are conscious of the almost cavalier manner in which antibiotics have been prescribed over decades regardless of patient characteristics, it is satisfying to find at last a paper suggesting adjusting the dose of antimicrobial agents for bodyweight in adults (Falagas and Karageorgopoulos, 2010). To assist with this approach, pharmaceutical scientists (Mehuys et al., 2010) suggested that a 8-fold divisible tablet formulation as an ideal form for achieving more precise dosing. Pharmacists often have not had the appropriate tools

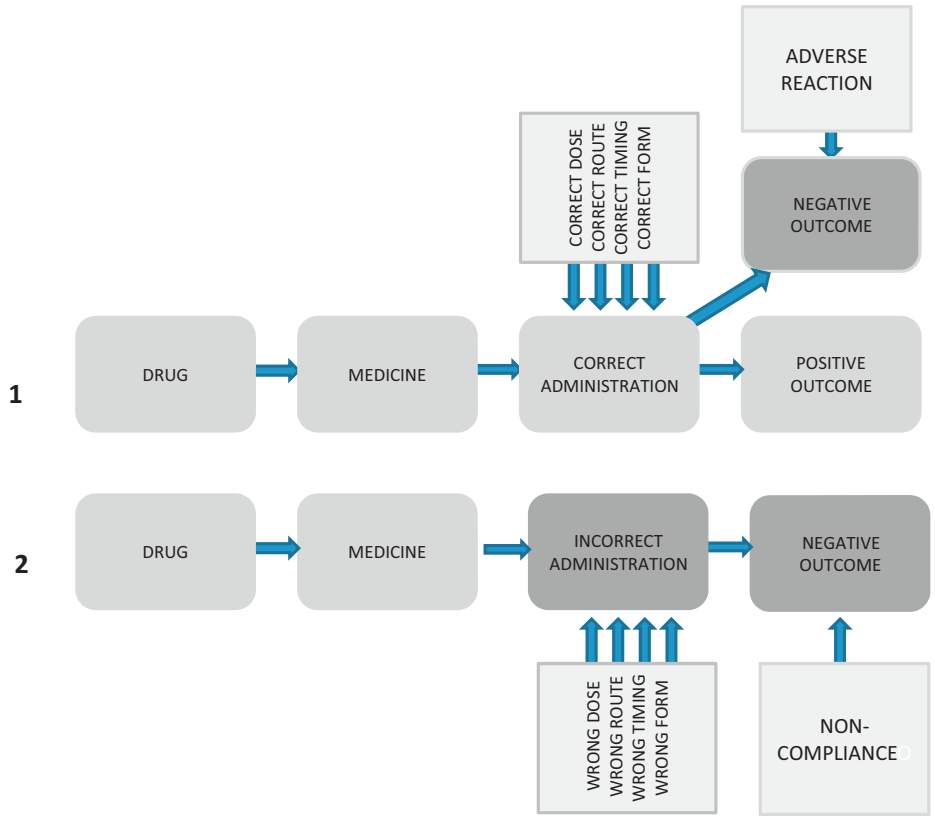

Fig. 2. Flow line 1 shows the potential with the correct drug, formulated as a medicine and then correctly administered, likely leading to a positive outcome. Flow line 1 has, however, a branch which leads to a negative outcome due to adverse reactions and events. In the future the susceptibility of patients to adverse effects should be better understood. Flow line 2 refers to the situation which occurs due to incorrect administration, more prevalent than the lay person would imagine: wrong dose, wrong route, wrong timing, wrong form of medication, and non-compliance by patients or carers leading clearly to negative outcomes.

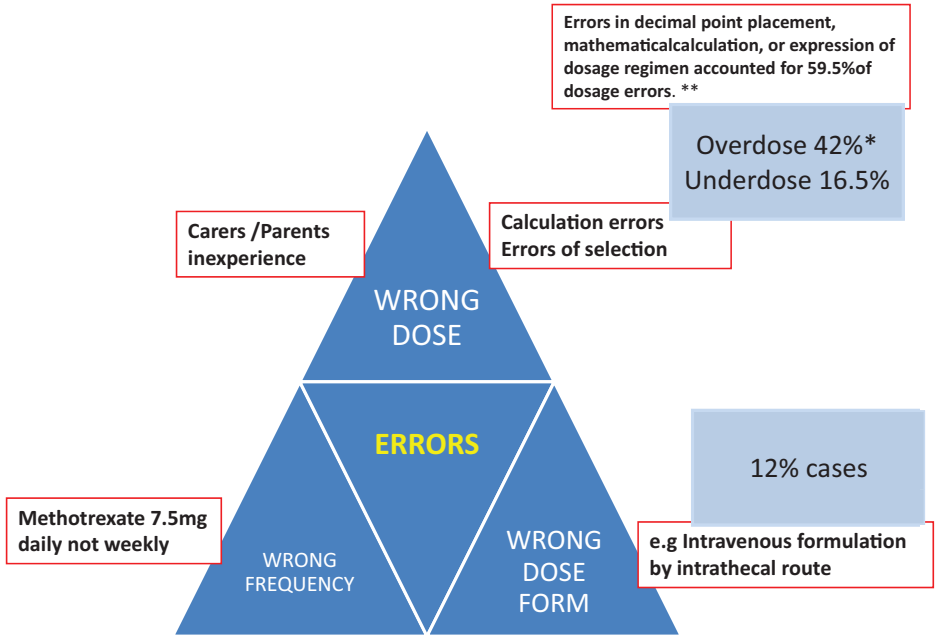

Fig. 3. . Errors of medication (neglecting the issue of the wrong or inappropriate drug): wrong dose, wrong frequency and wrong dose form (or wrong use of a dosage form) as in Schier et al. (2003), or Hider (2000). Some documented examples are indicated. See also Lesar et al. (1995).

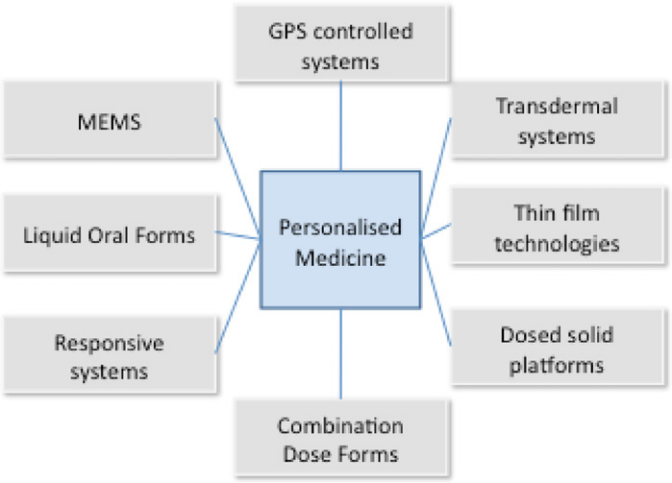

Fig. 4. Delivery possibilities to aid the application of personalised medicines.

to provide such solutions or to perfect a second line of defence, especially in community practice, but as Wening and Breitkreuz (2011) have indicated there are many potential delivery solutions. But there needs to be a concerted effort to allow physicians and pharmacists to share patient physiological and other critical data and for manufacturers to provide proper PK/PD information on their products. In secondary care, the intervention of clinical pharmacists has had clearly documented benefits (Koren et al., 1991).

Nevertheless, there is much room for improvement as the prevalence in hospital practice of errors and omissions that lead to adverse events shows (Lewis et al., 2009). As can be seen from Fig. 3, 42% of reported errors in some wards involved overdosing, and 16.5% underdosing. The importance of levodopa dose and dosage regimen in Parkinson's disease is reviewed by Goole and Amighi (2009). Clearly, if personalised medicine is to build on the success of the science involved in drug design and choice, then much has to be done to ensure that there are appropriate means of delivering drugs pharmaceutically, physically and appropriately to patients convinced of the need to take their medication.

Individualised dose forms and other means will allow us to come closer to personalised medicine (Fig. 4), provided patient information is correctly shared. There are many formulation and device approaches that may return to pharmacy of an earlier era when "The Mixture" was intended for one patient and no other. There is a resurgence in the United States of compounding pharmacies which can transform unsuitable medicines into a wide range of forms and scaled doses. Many flexible dosing system are now available, from mini-tablets and their dispensing devices (Bredenberg et al., 2003), to patient-controlled analgesic delivery pumps, adding to delivery methods which offer more flexible dosing increments than the traditional discontinuous dosage (e.g. 2.5, 10, 25, and 50) progression. Existing controlled release systems move us part of the way, but these themselves can be a source of errors and confusion (Lesar, 2002). One reason lies in the complexity of dealing with multiple modified release preparations of the same agent. In the UK in 2000 of eight once-daily preparations of diltiazem the lowest daily dose ranged from 120 mg to 240 mg, the highest dose from 300 to 500 mg. With nifedipine four products had the following three different once-daily dose ranges 20–90, 30–90, 40–80 mg). We should not forget the positive potential of formulation to improve the quality of medication, but must be midful also of their potential to be the cause of adverse reactions and events (Uchegbu and Florence, 1996).

7. Enhanced drug delivery

Now there is the prospect with technologies such as three-dimensional printing to have pharmacy-based fabrication of precise dose tablets and other forms. The use of other technologies, such as telemedicine to control insulin pumps (Gröning et al., 2007) or remote controlled capsules (Pi et al., 2009) brings medication to an exciting phase. Fig. 4 suggests some of these possibilities.

Bar-coding of products can lead to minimisation of some medication errors (Poon et al., 2010a,b; Kerr et al., 2010), particularly those which ensue from transcription of orders, medicine administration and errors of timing of administration. The technology developed to avert the use of counterfeited medicines by implanting markers in tablet coatings, for example, (®mark® On-dose ID) could perhaps be extended to ensure that individual doses are dispensed to the correct patient.

8. Conclusions

The personal element of personalised medicine must not be overshadowed by wizardry. One must agree with Møldrup (2009) who argues for the "necessity of a more holistic view of individualised medicine without equating it to pharmacogenetics" and with Steele (2009) who said "the ability to precisely describe phenotypes has allowed us to change the specific but not the fundamental practice of medicine", and we might add, of pharmacy too. The therapeutic renaissance demands better understanding of diseases, better understanding of hurdles to target, better appreciation of monitoring as well as use of modelling and simulation. There are still many hurdles to the evolution of personalised medicine, not only technical but also professional and financial. The use of more tailored therapy means that markets for certain medicaments become smaller, but effectiveness will increase, hence the benefit to the population at large while to industry it decreases. Is this a soluble paradox? It will certainly defeat the object if the cost of so-called personalised medicines is unaffordable to the majority. Health-care professionals need more assistance in sharing information such as key patient parameters that affect absorption distribution and metabolism of drugs, full information on the properties of dose forms in a variety of patients and much more. This requires the more meaningful cooperation of the pharmaceutical industry and the regulatory bodies.

Little of this is new, which reflects the inertia that exists in health care systems and professions. Cohen's (1999) observation that individualised doses and common sense are key to avoiding problems in drug therapy stands today. There are few excuses given the technologies that we possess.

References

Biesecker, L.G., 2009. American Society of Human Genetics, 59th Annual Meeting. Press briefing (Medscape Medical News) (www.medscape.com).
Bredenberg, S., et al., 2003. An automatic dose dispenser for micro-tablets—a new concept for individual dosage of drugs in tablet form. Int. J. Pharmaceut. 261, 137–146.
Chan, M., Nicklason, F., Vial, J., 2001. Adverse drug events as a cause of hospital admission in the elderly. Intern. Med. J. 31, 199–205.
Chisholm, M.A., Mulloy, L.L., DiPiro, J.T., 2005. Comparing renal transplant patients adherence to free cyclosporin and free tacrolimus immunosuppressive therapy. Clin. Transplant. 19, 77–82.
Cohen, J.S., 1999. Ways to minimse adverse drug reactions. Individualised doses and common sense are key. Postgrad. Med. 106, 171–172.
Cutler, D.M., Everett, W., 2010. Thinking outside the pillbox—medication adherence as a priority for health care reform. N. Engl. J. Med. 362, 1553–1555.
Falagas, M.E., Karageorgopoulos, D.E., 2010. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet 375, 248–251.
Ferrer, R.E., Anron, C., 1998. Increase in US medication error deaths. Lancet 351, 1655–1656.
Florence, A.T., 2008. Neglected diseases, neglected technologies, neglected patients? Int. J. Pharmaceut. 350, 1–2.

Fogg, J., 1965. Errors of medication in hospital. Lancet 286, 31–32.
Goole, J., Amighi, K., 2009. Levodopa delivery systems for the treatment of Parkinson's disease: an overview. Int. J. Pharmaceut. 380, 1–15.
Gröning, R., Remmerback, S., Jansen, A.C., 2007. Telemedicine: insulin pump controlled via the Global System for Mobile Communications (GSM). Int. J. Pharmaceut. 39, 61–65.
Hazel, L., Shakir, S.A.W., 2006. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 29, 385–396.
Hider, J.D., 2000. Effectiveness of modified release isosorbide mononitrate affected by incorrect use. Br. Med. J. 320, 483.
Kerr, G.J., Heelon, M., Higgins, T., 2010. Bar-coding technology to reduce medication errors. N. Engl. J. Med. 363, 698.
Knibbe, C., Danhof, M., 2011. Individualized dosing regimens in children based on population PKPD modelling: are we ready for it? Int. J. Pharmaceut., this issue.
Koren, G., Reich, A., Hales, B., 1991. Use of clinical pharmacists to prevent medication errors in children. J. Pharm. Technol. 7, 219–221.
Lee, V.H.L., 2010. Personalized medicine: transforming drug development and healthcare. Ther. Deliv. 1, 615–619.
Lesar, T.S., 2002. Prescribing errors involving medication dosage forms. J. Gen. Int. Med. 17, 579–587.
Lesar, T.S., Briceland, L.L., Delcourse, K., et al., 1995. Medication prescribing errors in a teaching hospital. JAMA 263, 2329–2334.
Lewis, P.J., Donan, T., et al., 2009. Prevalence, incidence and nature of prescribing errors in hospital inpatients; a systematic review. Drug Saf. 32, 379–389.
Mehuys, A., Kayitare, E., Vervaet, C., Remon, J.-P., 2010. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet 375, 983–984.
Møldrup, C., 2009. Beyond personalized medicine. Pers. Med. 6, 231–233.
Phillips, D.P., Christenfeld, N., Glyn, L.M., 1998. Increase in US medication error deaths between 1983 and 1993. Lancet 351, 643–644.
Pi, X., Liu, H., et al., 2009. A novel remote controlled capsule for site-specific delivery in human GI tract. Int. J. Pharmaceut. 382, 160–164.
Poon, E.G., Keohane, C.A., Yoon, C.S., et al., 2010a. Effects of bar-code technology on the safety of medication administration. N. Engl. J. Med. 362, 1698–1707.
Poon, E.G., Churchil, W.W., Gandhi, T.K., 2010b. Bar-code technology to reduce medication errors. N. Engl. J. Med. 363, 698.
Raju, T.N.K., Keckes, S., Thornton, J.P., Perry, M., Feldman, S., 1989. Medication errors in neonatal and paediatric intensive care units. Lancet 334, 374–376.
Schier, J.G., Howland, M.A., Hoffman, R.S., Nelson, L.S., 2003. Fatality from administration of labetalol and crushed extended release nifedipine. Ann. Pharmacother. 37, 1420–1423.
Steele, F.R., 2009. Personalized medicine: something old, something new. Personal. Med. 6, 1–5.
Uchegbu, I.F., Florence, A.T., 1996. Adverse drug events related to dosage form and delivery systems. Drug Saf. 14, 39–67.
Vere, D.W., 1965. Errors of complex prescribing. Lancet 285, 370–373.
Wening, K., Breitkreuz, J., 2011. Oral drug delivery for personalised medicine: unmet needs and novel approaches. Int. J. Pharmaceut. 404, 1–9.