BMJ LONDON, SATURDAY 14 SEPTEMBER 1991

How to pay for expensive drugs

Pitting hospitals against general practices is not the answer

Recently the *BMJ* has highlighted the problems of prescribing expensive drugs, such as interleukin 2 and erythropoietin, for NHS patients.[1,2] The problems seem likely to get worse. Ondansetron may be better than other antiemetics in some patients receiving cancer chemotherapy, yet even specialist hospitals cannot afford to prescribe it for all those likely to benefit. Centoxin, which reduces mortality in patients with Gram negative septicaemia,[3] costs £2200 for a single dose. Octreotide, recently marketed for patients with the carcinoid syndrome and other gastroenteropancreatic tumours, costs the NHS £950 a month if used at its highest recommended dose.[4] Granulocyte colony stimulating factor costs £395 for five vials; other expensive cytokines will surely follow.

Drug costs, however, shouldn't be considered in isolation. For example, isotretinoin is undoubtedly expensive (costing up to £350 for a four month course), but over five years the total costs of treating patients with acne are less in those given isotretinoin, quite apart from its greater efficacy.[5] Considerations of relative efficacy can guide choice—for example, large trials have shown no substantial difference between the thrombolytic effects of tissue plasminogen activator and streptokinase despite a 10-fold difference in cost.

Because many of these expensive new drugs, used properly, represent important therapeutic progress we need to have strategies for dealing with them. The NHS is not and never can be a bottomless pit, ever able to respond to the latest expensive medical advance. How then should we decide to spend its limited resources? For many years hospitals have trimmed their expenditure in the face of shrinking resources by attacking the drug budget, but that approach has just about run its course. By now, most hospital drug and therapeutics committees have done everything in their power to hold down spending on drugs. Yielding to the temptation to have these committees financially driven rather than clinically led is not the answer.

The use of quality adjusted life years (QALYs), devised by health economists,[7] is one approach. While it may be valuable when considering coronary artery bypass grafting or hip replacements, applying it to the use of expensive drugs is more difficult. Other ways exist of affording these new and expensive drugs. The use of drugs—such as interleukin 2 or botulinum toxin, which may not have a product licence at the time of their use—should really be counted as research: their costs could therefore come out of the service increment for teaching and research (SIFTR). (The service costs of research in NHS hospitals have recently been added to the service increment for teaching.) Now is the right time to consider such changes as the whole topic of NHS research is under review.[8]

Although hospital formularies and generic prescribing have helped to contain the predicted increase in hospital drug costs,[9] most of the savings have come from transferring costs to the community, where the drug budget is not cash limited. This manoeuvre has previously caused problems for general practitioners, but these have increased since 1 April when fundholders acquired actual drug budgets and non-fundholders acquired indicative prescribing amounts. Hospitals' excessive limitation on how much medicine they give patients on discharge and their restrictions on prescribing in outpatient or accident and emergency departments also causes problems for local general practitioners. Better communications between hospitals and general practices would help. (The use of fax machines, however, has thrown up as yet unresolved medicolegal problems.[10])

Hospitals don't make the lives of general practitioners any easier by offloading the prescribing of expensive drugs—such as cyclosporin, erythropoietin, and growth hormone—on to them. In most of these cases general practitioners could hardly be said to be clinically responsible for this aspect of their patients' care. To make matters worse, hospitals often succumb to skilful marketing and choose for their formularies drugs that have been heavily discounted to them but that cost much more when prescribed in the community. As 80% of prescribing is done in the community such "loss leaders" may actually increase drug costs when viewed from a national perspective. When hospitals are revising their formularies they need to consult with their general practitioner colleagues and avoid placing in the formulary those drugs that appear to be loss leaders (provided all other therapeutic matters are equal).

Such cost effective approaches to treatment are now being encouraged. Clinical budgeting in hospitals has persuaded doctors to think more about the costs of what they do. *Improving Prescribing* (working paper 2 of *Working for Patients*) tells us to bring together hospital and community prescribing,[11] and the regional health authority provides the administrative machinery for doing so. As yet, however, we lack the necessary finances for this. When viewed nationally our use of drugs is inefficient, but for hospitals to take back the prescribing costs would be prohibitively expensive. To correct the problems that I have identified would cost about £3m a year in the Mersey region, about three quarters of this falling on the central teaching hospital. Savings to the overall regional drug budget would surely exceed that in the first

year, however, and from these cumulative savings we could begin to afford the new expensive drugs. Placing hospitals on the same footing as their community counterparts, who do not pay value added tax on drugs, would release additional funds.

More rational ways of using the nation's resources should be sought, and as a national problem it requires a national solution. The long term benefits of a solution—both financial and in improved working relationships—would handsomely repay any short term infusion of resources.

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More macrolides

Some may be improvements on erythromycin

Almost 40 years have elapsed since the first reports of the use of the macrolide antibiotic erythromycin in the treatment of human infections.[1] During this period it has established itself as one of the safest antibiotics in current use and an effective alternative to penicillin for the treatment of and prophylaxis against Gram positive infections of the skin, soft tissues, and respiratory tract.[2] It has also become the favoured agent of choice for treating infections caused by *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Legionella* sp. Indeed, with doctors' increasing awareness of the role of intracellular pathogens such as mycoplasma, legionella, and *Chlamydia pneumoniae*,[3] not only in pneumonia[4] but also in milder respiratory illnesses of all types, erythromycin has become the first line treatment for many respiratory illnesses acquired in the community.[5]

Erythromycin does, however, have several drawbacks related to its pharmacokinetics, microbiological activity, and tolerability. Because of its instability at a low pH the concentrations achieved in the blood after oral administration are erratic. Various oral preparations of erythromycin have been formulated to overcome this poor bioavailability, but little convincing evidence exists that these modifications are accompanied by any improvement in clinical efficacy. The main microbiological drawback of erythromycin is its inadequate activity against *Haemophilus influenzae*. A recent survey found that one in six isolates of *H influenzae* from England and Scotland had high level resistance to erythromycin,[6] precluding sole reliance on erythromycin when *H influenzae* is a likely pathogen. Finally, compliance with erythromycin treatment is often poor. Part of the problem is that it is usually prescribed in a six hourly regimen; once or twice daily regimens are generally better adhered to.[7] An additional factor, however, is the frequent occurrence of nausea, epigastric discomfort, and other minor gastrointestinal symptoms, particularly in adults, after it is taken.[2]

Over the past decade the pharmaceutical industry has shown a resurgence of interest in the macrolides and a dozen or so derivatives have been undergoing development.[8] All these new macrolides are more stable in acid than erythromycin; many also have a longer half life or better microbiological activity, or both. The first of these new macrolides is now available in the United Kingdom and others may follow soon.

Roxithromycin is an ether oxime derivative of erythromycin and is already available in several European countries, although not in the United Kingdom. It has a long serum half life, allowing twice daily administration, but otherwise few advantages. What is gained by higher plasma concentrations is lost by lower in vitro antimicrobial activity than erythromycin against most organisms.[9] Flurithromycin has a similar range of activity but has only 25-50% the potency of erythromycin.[8] Dirithromycin is an oxazine derivative of erythromycin with a half life of over 24 hours and excellent tissue penetration. Its range of activity is similar to that of erythromycin but with less activity against Gram positive bacteria and somewhat better activity against Gram negative organisms. Clinical assessments are not yet available.

Azithromycin is the first of a new group of 15 membered ring macrolides referred to as the azalides. It, too, is less active against Gram positive bacteria but considerably more active against *H influenzae* than erythromycin.[10] It is also effective in vitro against *Toxoplasma gondii* and *Mycobacterium avium-intracellulare* and may be more effective against legionella than erythromycin.[11] It is more stable in acid than erythromycin. Its serum half life is eight to 16 times longer than that of erythromycin, and the tissue concentrations are considerably higher than the serum concentrations and persist for several days after dosing.[12]

The clinical importance of this divergence between serum and tissue concentrations needs clarification. The criteria on which to decide whether an organism is sensitive or resistant and the types of infection to treat are still uncertain. Some studies have suggested that for certain organisms the tissue concentrations are more important.[13] This may be particularly important in intracellular infections: one study suggests that a single dose of azithromycin may be effective in chlamydial urethritis.[14] This may not be the case for other infections: poor results were obtained against *H influenzae* in exacerbations of chronic bronchitis, for instance, despite high sputum concentrations,[15] and fears exist that the low serum concentrations may be detrimental in the treatment of infections such as pneumococcal pneumonia in which septicaemia is frequent.

Clarithromycin is a new, orally absorbed 6-*O*-methyl derivative with a similar range of activity to that of erythromycin. Launched in Ireland and Italy last year, it has now become the first of the new generation of macrolides to be introduced in the United Kingdom. After oral administration it is converted to a 14-hydroxy metabolite.[16] The parent compound has similar activity to that of erythromycin against *H influenzae*, but the metabolite is twice as active,[10 16] and combinations of clarithromycin and 14-hydroxy-clarithromycin, in ratios achievable in vivo, show varying