The choice of administration route for an antibiotic remains a fairly controversial matter, as confirmed by the variation in prescribing habits among different countries. This variation may result from difficulty in identifying standard criteria that would unequivocally indicate the necessity of oral or parenteral administration. In general, the decision to administer an antibiotic by the parenteral route is influenced by three main factors: (i) reduced gastrointestinal absorption in the patient; (ii) lack of appropriate oral antibiotics; and (iii) specific disease and related severity.

Although relatively rare, gastrectomy and short-bowel syndrome are the main gastrointestinal conditions that make oral administration impossible. Diarrhoea, nausea and vomiting are the most frequently observed gastrointestinal side effects that occur as a result of oral administration of an antibiotic; these disturbances can be responsible for impaired absorption. Such side effects vary greatly in incidence and intensity according to the class of antibiotic used, but they should never be underestimated as they may lead to reduced compliance and/or gastrointestinal absorption which modifies the bioavailability of the drug and so may affect the outcome of treatment. For example, it has been reported that about 10% of 32,000 patients treated with co-amoxiclav, one of the most commonly prescribed antibiotics worldwide in an outpatient setting, experienced a gastrointestinal disorder.

Aminoglycosides, carbapenems and glycopeptides are the main classes of antibiotics for which no oral formulation is available. Whenever aetiology and/or clinical considerations make their use mandatory, the parenteral route of administration is unavoidable.

Because of the risk of early complications, parenteral antibiotic therapy is always necessary from the outset in some infections such as endocarditis, osteomyelitis or meningitis, but in general the choice of parenteral therapy is reserved for more severe infections. This is in accordance with the belief that an injectable antibiotic, especially when used intravenously, guarantees rapid achievement of high blood concentrations, whereas oral administration does not. However, many drugs are absorbed very well, so adequate blood concentrations can be achieved by oral administration. More recently, MacGregor & Graziani have proposed that, for serious infections, oral administration of antibiotics, especially at high doses, can offer a rational alternative to the parenteral route. However, they failed to point out that the incidence and severity of gastrointestinal side effects are important drawbacks of such a practice. Choice of the parenteral route remains an empirical and individual decision which is generally associated with hospitalization.

A European survey, conducted by Halls, of the management of infections in hospitals in different countries, showed that Italy had the highest proportion (82%) of injectable therapies with 45% given by the intramuscular route, far exceeding the proportions in other countries (≤50%). In Italy, the number of both initial therapy failures and failures upon completion and requirement for admission to other hospitals or departments was significantly lower than the European average. Although several factors should be considered in assessing the final result of antibiotic therapy in hospital (such as the duration of therapy, the length of hospital stay, the drug and dosage, and the severity of the disease), it is tempting to speculate that the common use of parenteral antibiotics might explain the significantly improved outcome of antibiotic treatments in Italy.

However, it should also be noted that in Italy, 53% of outpatient lower respiratory tract infections (LRTI) are treated with parenteral antibiotics, compared with 10% in France, 8% in Spain, 1.2% in Germany and 0.2% in the UK. Recourse to further diagnostic investigations and the number of hospitalizations also vary considerably among European countries. This probably reflects not only a different view of the criteria for disease severity, but also, the customs and rules governing the use of parenteral antibiotics, which affect the prescribing behaviour of

Outpatient parenteral treatment of bacterial infections: the Italian model as an international trend?

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As a result of extensive clinical experience of OPAT acquired in the USA, other countries (such as Canada, Germany, the UK, Australia, The Netherlands) have taken this therapeutic approach on board and have set up home parenteral therapy programmes or models. Canada and the USA were the first to develop their own guidelines to adapt OPAT for local use.

More recently, following a workshop held in London in 1997, a multidisciplinary group of experts, including primary care physicians, microbiologists, nurses, pharmacists and other professionals involved in the management of infections by parenteral home infusion therapy (OHPAT), provided very clear guidelines, defining strategies and programmes suitable for the UK.13

The guidelines available in different countries do not differ substantially from one another with regard to patient selection, amenable diseases and the professional team involved in home therapy and monitoring. All the guidelines include the self-administration model, performed by patients themselves or by a family member as a therapeutic programme option.14,15 This model offers considerable benefits in terms of cost saving, given the reduction in professional staffing costs.

The self-administration model is, thus, particularly interesting. It is probably already widely used in other countries, though in different ways and without well-codified or well-defined therapy programmes.

In Italy, home parenteral therapy has become accepted because of the improvements in quality of life, which have been amply documented in the USA (such as reduction in hospitalization trauma in children or in immobilization syndrome in the elderly), and the alternative of home parenteral therapy for patients who would otherwise need hospital treatment.10–12 The clear economic benefits, the main factor behind the development of OPAT in the USA, have paradoxically played only a secondary role in Italy, and are only now receiving due consideration.

Though constrained by the lack of standard criteria for patient selection and well-defined therapeutic protocols, the Italian model of OPAT is also characterized by the home treatment of infections of moderate severity, mainly LRTI. Compared with other countries, there is less use of broad-spectrum antibiotics (chiefly β-lactams), administered intramuscularly, for other infections such as bone and joint sepsis, and skin and soft tissue infections. The selection of patients for OPAT remains an individual decision of GPs based on the severity of the infection, concomitant diseases, age of the patient, reliability of patients and family, and environmental and social factors. If ancillary therapeutic services, such as oxygen support, physiotherapy and laboratory monitoring, are necessary, hospitalization is generally preferred, with the patient being discharged early, if possible.

This system has gained broad support over the years from patients in Italy because (i) home is seen as better than hospital, even when one is ill; and (ii) parenteral drugs are perceived as more effective than oral ones. This is probably in contrast to the culture and traditions of other countries (especially those in northern Europe) where hospitals are still considered the only proper site of care and intramuscular administration is much less acceptable.

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### Table. Rules and customs regarding the use of injectable antibiotics in different countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Administration of injectable antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>GP can prescribe; injections can be given by GP or nurse; both are reimbursable</td>
</tr>
<tr>
<td>Germany</td>
<td>GP can prescribe; injections can be administered only by GP; GP has a limited budget for pharmaceutical expenses, but not for complementary diagnostic procedures</td>
</tr>
<tr>
<td>Italy</td>
<td>GP can prescribe; intravenous injections can be given only by GP, even at the patient’s home; intramuscular antibiotics can be self-administered</td>
</tr>
<tr>
<td>UK</td>
<td>GP can prescribe, but does not usually do so; injections can be given by GP or nurse only; antibiotic and sanitary costs are reimbursable</td>
</tr>
<tr>
<td>USA</td>
<td>GP can prescribe; antibiotics can be self-administered; healthcare insurance refunds antibiotic and doctor’s or nursing expenses</td>
</tr>
</tbody>
</table>

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As regards the choice of antibiotics to be used, not even the national OPAT programmes established by Study Commissions (in USA, Canada and The Netherlands) have proposed guidelines. This choice is an integral part of the individual therapy programme and guidelines should be locally rather than nationally based.

The main class of antibiotic used in Italy is the cephalosporins: of 53 million antibiotic prescriptions given to outpatients in Italy in 1996, about 5 million were for injectable third-generation cephalosporins. The reason for such widespread use of third-generation cephalosporins is likely to lie in their microbiological, pharmacokinetic, pharmacoeconomic and clinical properties, which meet the main requirements of an antibiotic for home parenteral therapy: spectrum of activity, tolerability and safety, compliance and cost.16–18

The antibacterial spectrum of third-generation cephalosporins covers most of the microorganisms responsible for community-acquired infections, except for atypical pathogens such as Mycoplasma and Chlamydia (macrolides are usually administered with cephalosporins whenever atypical respiratory pathogens are suspected). No clear evidence of bacterial resistance caused by the selective pressure of such antibiotics has emerged in Italy and France, which make more use of these drugs than other countries. For example, in a multicentre French study, Goldstein and colleagues reported that 5700 bacterial isolates obtained in the outpatient setting were fully susceptible to ceftriaxone, including 34% of penicillin-resistant Streptococcus pneumoniae, 25% of β-lactamase-positive Haemophilus influenzae and 36% of amoxycillin-resistant Escherichia coli isolates.19 Data from the Alexander Project, a multinational surveillance of bacterial resistance, show that in Italy the rates of resistance among most of the pathogens commonly responsible for LRTI, such as S. pneumoniae, H. influenzae and Moraxella catarrhalis, were significantly lower than those in other countries participating in the study.20–22

More recently, Marchese et al. maintained that the use of injectable antibiotics, by ensuring higher and more persistent tissue concentrations than orally administered drugs, could explain the low incidence of bacterial resistance in Italy among those pathogens responsible for community-acquired infections.23

Prolonged antibiotic therapy could also have a role in development of antibiotic resistance. In Italy treatments are less protracted than in other European countries (mean duration 6.6 ± 2.5 days for treatment of community-acquired LRTI compared with 8.5 ± 2.2 in France, to 8.6 ± 3.4 in Germany and with 8.6 ± 3.2 in Spain).7 Shorter courses of treatment could limit the selection of resistant microorganisms.

The safety and tolerability of the third-generation cephalosporins have been amply demonstrated by clinical practice, which has seen millions of treatments for a large number of diseases being carried out both in hospitals and in the community. Local pain after an intramuscular injection remains an uncommon complaint. No epidemiological data are available on the incidence of local abscesses resulting from intramuscular injection.24,25

Cephalosporins and other broad-spectrum antibacterial agents have long been thought to predispose to Clostridium difficile-associated diseases and the increase in C. difficile colitis in the world may result not only from previous underestimation but also from increased use of cephalosporins.26,27 However, there is no evidence of an increasing rate of colitis associated with the use of broad-spectrum antibiotics in Italy, nor are there data supporting a possible relationship between colitis and route of administration.

Home parenteral therapy has very clear economic benefits, in terms of both direct and indirect economic savings. One of the main reasons for the success of self-administration by intramuscular injection, which is widely employed in Italy and which has been successfully used in other countries with OPAT experience, such as USA and Israel,18,23 may be the greater ease involved in giving the treatment. In the USA, for example, the intramuscular route of antibiotic administration is considered important because it makes the OPAT option available to small primary care or family practices that are not equipped to provide intravenous infusion.15 This is potentially useful for patients who are young, working and otherwise healthy, and even for children.18

In conclusion, home antibiotic therapy is being used increasingly because of the clinical and economic advantages that it confers. The Italian Terapia Antibiotica Iniettiva Domiciliare (TAID) experience is thus viewed with considerable interest by other countries. It would be advantageous and desirable to increase the number of home parenteral treatments, improve existing therapy programmes or create new ones, and to define the criteria for selecting patients eligible for treatment so as to reduce the number of hospitalized cases and, at the same time, limit the excessive use of parenteral therapy when the latter is unnecessary.

References

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