Appendix II: How to use antibacterial agents in the elderly

The committee for The Japanese Respiratory Society guidelines in management of respiratory infections

The Japanese Respiratory Society

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CHANGES IN DRUG-METABOLISING CAPACITY IN THE ELDERLY

Physiological parameters change with an advancing age, and the elderly exhibit a unique pharmacokinetic profile as influenced by drug-related differences and individual differences after a process of drug interactions, such as interference, counter-balancing and drug-synergy.

Absorption

The pH of gastric juice rises in the elderly as a result of diminished gastric acid secretory ability, and their gastric juice tends to be only slightly acidic. The new macrolide antibiotics Roxithromycin (RXM) and Clarithromycin (CAM) are stable in slightly acidic gastric juice, and both are transferred to the small intestine without loss of antimicrobial activity, where they are absorbed, thereby contributing to high blood levels of these antibiotics. The biological activity of acid-labile antibiotics (such as penicillin) may also be enhanced by the high pH of gastric juice in the elderly.

In addition to these pharmacokinetic characteristics, drug absorption may be reduced or delayed in the elderly due to lowered rates of gastric emptying, diminished bowel movements, reduced area for absorption in the gastrointestinal tract and reduced small-intestinal blood flow.

Distribution

Two factors (i) changes in body composition and (ii) reduced plasma albumin levels, play an important role in drug distribution in vivo in the elderly. The unique feature of body compositions in the elderly is a higher fat content than in young individuals, and occasionally elderly persons have approximately twice as much adipose tissue as young individuals. On the other hand, net tissue content = [whole body tissue content]—[adipose tissue content]—[total body fluid] is somewhat diminished in the elderly. Thus, the volume for distribution of fat-soluble drugs increases with age, whereas the volume for water-soluble drugs decreases. The elderly tend to have lower plasma albumin concentrations, and for that reason the binding constants for drugs and plasma proteins decrease in the elderly, resulting in increases in concentration of free form. As a result, the pharmacological actions of drugs are increased in the elderly, but there is a higher risk of adverse reactions.

Metabolism

Most drugs are metabolised in the liver, and their metabolites are readily excreted by the kidneys in the urine. The wet weight of the liver decreases with advancing age, and hepatic blood flow decreases in the elderly. The activity of hepatic drug-metabolising enzymes, such as cytochrome P-450, is lower in the elderly, resulting in a slower rate of drug metabolism in the liver. Consequently, the blood concentration of drugs may be higher in the elderly.

It is difficult to detect ‘decreased hepatic function’ in the elderly by only monitoring routine biochemical tests such as GOT, GPT, ALP and LDH levels. When ICG 15-minute retention rates were determined in elderly subjects (in their sixties to eighties) without overt hepatic/renal disorders, those in their eighties had slightly lower drug excretion capacity in the liver.

Excretion

The kidneys are the most important organs for drug excretion, and the drugs are eliminated by glomerular filtration and tubular excretion and re-absorption. Renal blood flow decreases with age, resulting in
lower glomerular filtration rates and reduced excretion by the renal tubules. Because the muscle component of the body declines with age and creatinine production is lower in the elderly, their serum creatinine (Scr) levels are often normal (latent renal disorder) despite diminished renal function.

Because of this, creatinine clearance (Ccr) must be determined to accurately assess renal function in the elderly. Ccr declines with age, and those in their eighties drop below 50% of the Ccr of healthy young adults. Ccr declines further in the elderly in their nineties, and they should be regarded as having moderate renal failure. Scr Yasuda’s equation, shown below, allows Ccr to be estimated conveniently and the estimated values correlate best with the actual values of Japanese elderly.

\[
\text{Ccr} = \frac{(176 - \text{age}) \times \text{body weight}}{100 \times \text{Scr}} \quad \text{(for men)}
\]

\[
\text{Ccr} = \frac{(158 - \text{age}) \times \text{body weight}}{100 \times \text{Scr}} \quad \text{(for women)}
\]

**In Vivo Pharmacokinetics of Antibacterial Agents in the Elderly**

Attention needs to be paid to the fact that the body weight of the elderly has declined, making doses per kilogram of body weight higher in the elderly.

**Oral administration**

When maximum plasma concentrations (Cmax) were determined in studies of the pharmacokinetics of oral antibacterial agents in the elderly, no major difference in drug absorption was found between young adults and the elderly. However, prolonged plasma terminal half-life increases the area under the plasma concentration-time curve (AUC) and lower urinary excretion rates have been observed. These findings indicate that many antibacterial agents are excreted through the kidneys (so-called ‘renal-excretion-type’), and these pharmacokinetic profiles can be explained primarily by diminished renal function in the elderly.

New macrolides and new oral cephems can be administered to the elderly orally in the same manner as in adults. If fluoroquinolones are administered to the elderly, the drugs have a long half-life, indicating excellent absorption. However, their Cmax may be very high, and for that reason care should be exercised with regard to oral administration of fluoroquinolones in the elderly.

**Intravenous administration**

The pharmacokinetics of ‘renal-excretion-type’ antibacterials such as flomoxef (FMOX), cefotizoxime (CZX), cefotetan (CTT), cefotiam (CTM) and cepapiramide (CMP) have been extensively examined and all of them have been found to have half-life-values twice as long in the elderly as in adult. High blood levels of FMOX, CZX, CTT, CTM and CMP were maintained in the elderly, because their renal excretion was delayed due to diminished renal function with advancing age. The urinary excretion rates of FMOX, CZX, CTT, CTM and CMP were lower in the elderly than in adults.

By contrast, cefoperazon (CPZ) and cepapiramide (CPM) are ‘hepatic-excretion-type’ cephems, and the half-life of CPZ and CPM in the elderly was 1.7-fold and 1.8-fold, respectively, longer than in younger adults. Thus, the half-life of ‘hepatic-excretion-type’ cephems was less prolonged in the elderly than the half-life of ‘renal-excretion-type’ antibiotics.

**Intramuscular administration**

The pharmacokinetics of bekanamyacin (AKM), tobramycin (TOB) and carumonam (CRMN) were examined in the elderly following intramuscular administration. When the Cmax values were evaluated in elderly and adult subjects, after compensation for body weight they were found to be lower in the elderly, indicating that the absorption of intramuscularly administered (local i.m. injection) AKM, TOB and CRMN is lower in the elderly. Following intramuscular administration, the blood levels of drugs remain high and half-life was prolonged in the elderly, the same as after oral and intravenous administration.

**Use of Antibacterial Agents in the Elderly**

**Necessity of use of antibacterial agents**

Antibacterial agents (antibiotics) should be used to treat infectious diseases, and their prophylactic use should be restricted to certain circumstances, such as burns and surgery.

**Selection of the proper antibacterial agents**

Appropriate antibiotics must be selected and administered, taking the host’s condition, causative bacteria and characteristics (such as pharmacokinetic profile) of the antibacterial agents (antibiotics) into consideration.

It is preferable to use antibiotics with a narrow spectrum of antibacterial activity whenever possible. In principle, antibacterial agents should be selected for the elderly in the same manner as for adults. However, care should be exercised in regard to administration of antibiotics to the elderly, paying particular attention to adverse reactions.

The elderly are in ‘latent renal failure’ and aminoglycosides should be avoided as first-line antibiotics, because they are nephrotoxic. Third-generation cephems and carbapenems are often used as first-line antibiotics to treat ‘mild pneumonia’. However, not all elderly are ‘compromised hosts’, and care should be exercised in the selection of suitable antibacterial agents for the elderly. It is also important to treat
dehydration and improve the nutritional status of the elderly and care should be exercised in regard to systemic management by means of oxygen therapy and sputum aspiration.

**Route of administration, dosage and administration interval**

The routes of administration of antibacterial agents include per os, oral administration (p.o.), intramuscular administration (i.m.) and intravenous administration (i.v.). Suppositories and local (topical) therapy are also used. The route of administration of antibacterial agents should be selected according to the disease and severity rating of the pneumonia, and oral antibiotics should be restricted to the treatment of mild or moderate pneumonia. Occasionally, it is difficult to administer antibiotics to the elderly intravenously, and when it is, they may be administered intramuscularly or orally. Oral antibiotic preparations (microgranules) are also useful for elderly patients who are being tube fed.

It is important to minimise the duration of intravenous antibiotics to avoid ‘decreased ADL’ in the elderly, as new oral cephems and fluoroquinolones are used properly.

Generally speaking, the body weight of elderly patients is low, and ‘bedridden’ patients often weigh only 30–40 kg. The doses of antibiotics for children are calculated on the basis of mg/kg body weight, and a similar approach is needed for the elderly. The doses of antibacterial agents are generally determined based on the Cmax of the drug and the minimal inhibitory concentration (MIC) for causative bacteria. Based on the above, the dose of an antibacterial agent for the elderly, as a rule, should be approximately 50–70% of the dose for adults. As shown in Figure 3, minimal doses of antibacterial agents should be prescribed for the elderly.

When antibacterial agents are administered to the elderly, renal excretion is often delayed and the blood levels of drug remain high because many of them are the ‘renal-excretion-type’. For this reason, as shown in Figure 1, it is necessary to prolong the administration intervals proportional to the degree of reduction in renal function (i.e. creatinine clearance). Antibiotics for both injection and oral should generally be administered to patients over 80 years of age twice a day if the half-life in adults is short. The half-life of ceftriaxon (CTRX) is more than three hours in adults, and it should be administered to the elderly only once a day. Fluoroquinolones have slightly longer half-life values, and they should be administered to the elderly only once a day. Sparfloxacin (SPFX) has a half-life of 8 h or more in adults, making it necessary to administer SPFX to the elderly only once every other day.

**Duration of administration**

Antibacterial agents should be discontinued if the pneumonia is assessed as ‘cured’ by the treating physician based on the clinical findings, erythrocyte sedimentation rate (ESR), WBC (leukocyte) count, CRP and other clinical laboratory findings. In patients with mild or moderate pneumonia, antibacterial agents may be discontinued in approximately seven days if the patient no longer has a fever, and if there is little evidence of inflammation on the CXR or indicated by the CRP values, as long as the patient is able to ingest food. Parenteral antibiotics are indicated for elderly patients with underlying diseases and who have moderate or severe pneumonia and for those with severe pneumonia. These must be administered for 10–14 days.

**Adverse drug reactions**

There is a risk of adverse drug reactions in the elderly when large doses of antibacterial agents are unnecessarily administered for long periods or when concurrent therapy or concomitant drugs are administered simultaneously and result in drug interactions. There is also a risk of adverse drug reaction(s) because the host has been sensitised by antibacterial agents administered previously. In addition, the elderly may experience adverse drug reactions as a result of metabolic conversion or as a result of increased drug deposition in the body due to secondary renal excretion.

Care should be exercised in regard to administration of aminoglycosides, cephems and glycopeptides (such as vancomycin) to the elderly, as these antibiotics are known to induce renal toxicity in a dose-dependent manner. Aminoglycosides are known to induce eighth cranial nerve disorders, while fluoroquinolones and carbapenems induce central nervous system manifestations. Care should be exercised in regard to the occurrence of gastrointestinal...
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tinal symptoms, drug-induced fever, hemorrhagic diathesis and pseudomembranous colitis.

In recent years, fluorescence-labelled immune-adsorbent assay procedures have made it easy to monitor blood levels of aminoglycosides and glycopeptides, thereby proving their usefulness in the treatment of pneumonia.

Instructions for compliance in taking antibacterial agents

Because elderly patients often have multiple underlying disorders, several medications that have ‘different dose schedules’ are often prescribed for the elderly. This increases the risk of errors in taking medications among the elderly, presenting new problems. The elderly may forget to take their medication and their pneumonia may worsen as a result. Drug prescriptions must be kept to a minimum to improve compliance. An effort should also be made to develop new formulations that synchronise dosage schedules so that the elderly can take their drugs more easily. An attempt should also be made to simplify ‘administration methods’. In summary, patients and/or their family should be provided with proper instructions that enable them to understand the necessity of taking their medications properly.

REFERENCES