The Pharmacokinetics of the Anti
What Are The Cli

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Several of the recent advances in antiviral drug development indicated in drugs now available. There are four licensed influenza antiviral agents v administered orally, while zanamir is given as a dry powder that is self-ad drugs differ in terms of their pharmacokinetics, and how this knowledge adjustments in varying age groups and in pa

Introduction

Advances in antiviral drug development and in rapid diagnostic methods have resulted in more efficient management strategies in the treatment of influenza.[1] Several of these advances have been particularly due to the improved pharmacokinetic properties of the drugs now available.[2]

Four licensed antiviral agents indicated in influenza are now available: the adamantanes (amantadine and rimantadine) with activity against influenza A viruses but not influenza B viruses; and the newer class of neuraminidase inhibitors (zanamivir [Relenza®] and oseltamivir [Tamiflu®]), which have activity against both influenza A and B viruses.[3]

The Adamantanes: Amantadine and Rimantadine

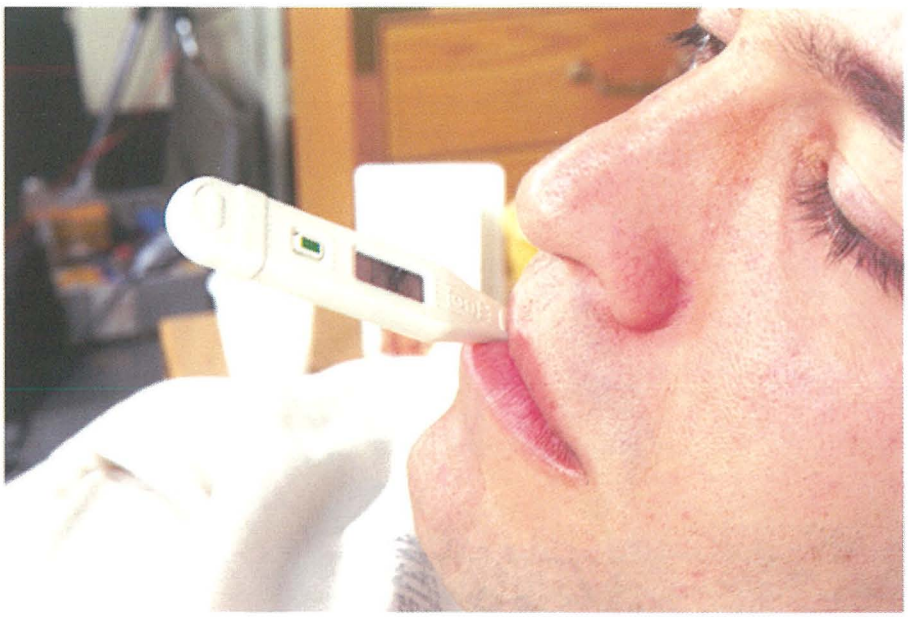
Amantidine is the oldest drug in this group having being marketed since 1966. Approximately 90% of amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion.[4] On the other hand, approximately 75% of rimantadine is metabolized by the liver and the apparent clearance of rimantadine has been found to be 50% lower for persons with severe liver dysfunction.[5] Rimantadine and its metabolites are then excreted by the kidneys.

Reduction in doses with amantadine and rimantadine are thus recommended in patients with any degree of renal insufficiency, but no reduction in dosage is recommended on the basis of age alone.[6]

The Neuraminidase Inhibitors: Zanamivir And Oseltamivir

Although related in terms of their mode of pharmacological activity, these two drugs have very varying pharmacokinetic parameters.

Zanamivir shows poor oral bioavailability in human volunteers, and in fact is administered as a dry powder using an oral inhaler. Zanamivir thus becomes highly



concentrated in the respiratory tract: 10 to 20 % reaches the lungs, and the rest is deposited in the oropharynx.[7] Five to 15 % of the total dose is then absorbed and excreted in the urine, resulting in a relative bioavailability of about 2%, with a half-life of 2.5 to 5.1 hours,[8] a feature that is potentially advantageous in situations in which a systemic drug is undesirable.[3]

This poor bioavailability, however, may be a problem in patients for whom inhalation may be difficult or when it is necessary to deliver the drug to sites of viral replication, as in cases of pneumonic disease.[8]

Population parameters for zanamivir have been estimated by a nonlinear mixed-effect modeling software program (NONMEM), using a one-compartment model with first-order absorption[9] Formulation and route of administration were found to be the most significant factors affecting the pharmacokinetics of zanamivir. No significant differences in pharmacokinetic parameters were observed when demographic variables, indices of infection, or concurrent medication use were considered in either phase I or phase II population analyses. Limited data is available regarding the safety and efficacy of zanamivir for patients with impaired renal function.[9]

Oseltamivir is really the ethyl ester prodrug of the active metabolite, oseltamivir carboxylate (GS4071 or Ro 64-0802).[10, 11, 12] Oseltamivir is efficiently converted to GS4071 after high and consistent site-specific absorption (around 80%) of both capsule and suspension formulations, from the gastrointestinal tract.[11, 12] This is an advantage of oseltamivir over zanamivir since the former achieves high plasma levels and thus can act outside the respiratory tract.

These studies also indicate that absorption is similar in the proximal and distal small bowel, but reduced from the ascending colon and they support the usefulness of a modified-release product.[12] Snell et al., found that the co-administration of various antacids with oseltamivir has no effect on the bioavailability or pharmacokinetics of either oseltamivir or the active metabolite.[13]

After conversion by hepatic carboxylesterases in the liver to the active metabolite, oseltamivir carboxylate, the latter distributes throughout the body, including the upper and lower respiratory tract.[10] Neither compound interacts with

viral Agents indicated in Influenza: nical Implications?

influenza have been due to the improved pharmacokinetic properties of the which are now available. Amantadine, rimantadine, and oseltamivir are ministered via oral inhalation. This brief review summarises how the four nay help to predict drug interactions and side effects, and estimate dosage tients with underlying pathological conditions.

cytochrome P450 mixed-function oxidases or glucuronosyltransferases.[14]

The active metabolite is detectable in plasma within 30 minutes and reaches maximal concentrations after 3 to 4 hours.[11] The pharmacokinetic profile of the active metabolite is linear and dose-proportional and it is 3% bound to human plasma proteins. After peak plasma concentrations are attained, its concentration declines with an apparent half-life of 6 to 10 hours. Steady-state plasma concentrations are achieved within 3 days of twice daily administration, and at a dosage of 75mg twice daily, the steady-state plasma trough concentrations of the active metabolite remain above the minimum inhibitory concentration for all influenza strains tested.[11] Exposure to the active metabolite at steady-state is approximately 25% higher in elderly compared with young individuals; however, no dosage adjustment is necessary. The pharmacokinetics in patients with influenza are qualitatively similar to those in healthy young adults

The active metabolite is eliminated through the kidneys by a first-order process as the unchanged drug by glomerular filtration and tubular secretion by an anionic transporter system.[10, 15] Given these characteristics, its potential for adverse interactions with other drugs appears limited to those arising from competitive inhibition of excretion by the renal tubular epithelial cell anionic transporter. In patients with renal impairment, metabolite clearance decreases linearly with creatinine clearance.[10]

Oo et al., assessed the metabolic and excretory capacity of oseltamivir and its active carboxylate metabolite in young children and the results demonstrated that infants as young as one year old can metabolize and excrete oseltamivir efficiently.[16]

Conclusion

This brief review has shown the importance of pharmacokinetics parameters when considering the choice, dosage, duration of therapy and use of influenza antiviral medications. During the decision making process, clinicians should also take into account the patient's age, weight, renal function, presence of other medical conditions and the potential for interaction with other medications.

No published data is as yet available concerning the safety or efficacy of using combinations of any of these four influenza antiviral drugs. Future investigations may also help to clarify the therapeutic role and pharmacokinetic advantages of novel antiviral drugs and formulations still in the development phase.

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