NELFINAVIR IN CHILDREN

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Welcome to Kiddies Corner. We hope that this will become a regular feature in our Journal. At HIV conferences and in the literature, paediatric HIV is sorely neglected. We hope that Kiddies Corner will be a forum where we can discuss all aspects of paediatric HIV infection. In this regard, we would like to draw your attention to our Internet-based discussion group, the Southern African HIV Clinicians Society Paediatric Discussion Group (PDG). This PDG has been in operation since late last year and is popular for helping to resolve clinical problems and for exposing paediatricians to the complexities of antiretroviral therapy (ART) in children. Anyone who is not yet on the mailing list and would like to join the PDG is welcome to send his or her e-mail address to leonlevin@54.co.za.

In our Guidelines for Antiretroviral Treatment in Children published in the November edition of this journal,[1] a printer's gremlin crept in (see Erratum, p. 6, Southern African Journal of HIV Medicine, February 2001). The jist of the error was to make it appear that there is no paediatric formulation for nelfinavir (NFV).

Since we were planning to discuss the individual antiretroviral agents in paediatrics, we thought that by starting with NFV we could set the record straight.

Nelfinavir (NFV) (Vira-cept; Roche) belongs to the class of protease inhibitors. It is a very useful drug for a number of reasons, although its high cost frequently limits its use.

1. NFV is extremely well tolerated in children, its only adverse effect of note being diarrhoea, which often resolves spontaneously or responds to commercial antidiarrhoeals. Only very seldom is it necessary to stop the NFV.[2,3]

2. NFV has a unique resistance profile which makes it ideal as a first-line agent. The first mutation that appears when resistance occurs is the D30N mutation.[4,5] This mutation does not confer resistance to any other PI. If NFV continues to be used in this setting, secondary mutations occur which do confer cross-resistance to other PIs.[6] Theoretically therefore (and also borne out by a few studies),[7-9] if there is failure of a NFV-containing regimen due to resistance and a change is made early on, there should be a good response to the other PIs or to a dual PI regimen.

3. Although lipid abnormalities and lipodystrophy do occur with NFV, there is some evidence that it is less common with NFV than with the other PIs.[10-12]

It is therefore evident that NFV is excellent as part of a first-line regimen. If a child is started on another PI and resistance develops, there is no point in changing to NFV as there will already be cross-resistance present. The only barrier preventing the use of NFV for first-line treatment is its prohibitive price.

The cost is exacerbated by the relatively high doses needed in children. The standard dose recommended by Roche is 20 - 30 mg/kg/dose 8-hourly.[2] However, recent studies have suggested that this dosage results in inadequate levels.[13] Hayashi *et al.*[14] found that a dosage of 55 mg/kg/dose 12-hourly results in adequate levels. A small study confirmed the efficacy of this 12-hourly dosing in 11 subjects.[15] Further studies, however, have suggested that 12-hourly dosing may be problematic in children, and a dose of 35 - 45 mg/kg/dose 8-hourly in children over 2 years of age and 45 - 55 mg/kg/dose every 8 hours in children under 2 years has therefore been suggested (Professor Courtney Fletcher – personal communication). Although there are as yet no good data, preliminary pharmacokinetic studies suggest that if the 12-hourly dose of NFV is preferred, a small dose of ritonavir (Norvir; Abbott) (100 mg/m^2/dose 12-hourly) be added to boost the NFV levels (Fletcher – personal communication).

Now that we have resolved the dosing issue, what about the paediatric formulation? NFV comes in two dosage forms, a 250 mg tablet and a powder for suspension. The strength of the powder is 50 mg/1 gram scoop. This means that every gram of powder contains only 50 mg

NFV, i.e. 95% of the product is inactive powder. Children often have a great deal of difficulty in tolerating the excess powder. As can be seen from Fig. 1, the crushed tablets yield much less powder and are therefore much better tolerated.[16] The potential benefit of increasing doses in smaller amounts is offset by the greater adherence to treatment with the crushed tablets. Because of the wide dosage range, it is usually possible to tailor dosage to the nearest tablet or half tablet. The crushed tablets can be administered with pudding, or the whole tablets can be dissolved in water to produce a dispersion that can be mixed with milk or chocolate milk.[17] As a result, most paediatric experts overseas are no longer using the powder formulation but have opted for the tablets instead.

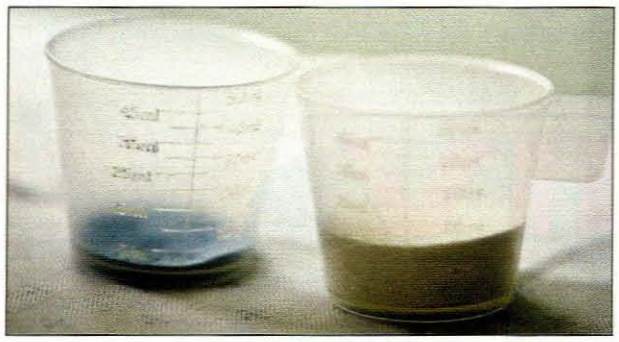

Fig. 1. Both containers contain 500 mg nelfinavir. The blue powder on the left is from two crushed 250 mg tablets, while the white powder on the right is 10 scoops of nelfinavir powder for suspension.

In conclusion, NFV remains a useful protease inhibitor in children. Its position is ideally 'first line', it is generally well tolerated, and the tablets are the formulation of choice. The 'package insert' dosage is too low, especially in children aged under 2 years, and twice-daily dosing is still unproven. The only real barrier to its more widespread use is its price.

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REFERENCES

1. Southern African HIV Clinicians Society Guidelines for Antiretroviral Therapy in Children. *Southern African Journal of HIV Medicine 2000;* Issue 2, pp. 19-30.
2. Viracept (Rm) (nelfinavir mesylate): prescribing information, Agouron Pharmaceuticals Inc., La Jolla, Calif., 24 Nov 1999.
3. Bardsley-Elliot A, Plosker GL. Nelfinavir. An update on its use in HIV infection. *Drugs* 2000; **59**(3): 581-620.
4. Patick AK, Mo H, Markowitz M, *et al.* Antiviral and resistance studies of AG1343, an orally bioavailable inhibitor of human immunodeficiency virus protease. *Antimicrob Agents Chemother* 1996; **40:** 292-297.
5. Patick AK, Duran M, Cao Y, *et al.* Genotypic and phenotypic characterization of human immunodeficiency virus type 1 variants isolated from patients treated with the protease inhibitor nelfinavir. *Antimicrob Agents Chemother* 1998; **42:** 2637-2644.
6. Hirsch MS, Conway B, D'Aquila RT, *et al.* Antiretroviral drug resistance testing in adults with HIV infection: implications for clinical management. *JAMA* 1998; **279:** 1984-1991.
7. Haubrich R, Kemper C, Witt M, *et al.* Differences in protease inhibitor (PI) phenotypic susceptibility after failure of the first PI-containing regimen (abstract No. 1167/oral presentation). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 26-29 Sep 1999, San Francisco.
8. Virologic responses to a ritonavir-saquinavir-containing regimen in patients who had previously failed nelfinavir. *AIDS* 1999; **13**(2): F23-F28.
9. Zolopa A, Tebas P, Gallant J, *et al.* The efficacy of ritonaivr (RTV)/saquinvir (SQV) antiretroviral therapy in patients who failed nelfinavir (NFV): a multicenter cohort study (abstract No. 2065). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 26-29 Sep 1999.
10. Nelson MR, Moyle G, Newell A. The incidence of hyperlipidaemia with protease inhibitors (PI) (abstract No. I-87). 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, 24-27 Sep 1999.
11. Keruly JC, Mehta S, Chaisson RE, *et al.* Incidence of and factors associated with the development of hypercholesterolemia and hyperglycemia in HIV-infected patients using a protease inhibitor (abstract No. I-95). 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, 24-27 Sep 1998.
12. Pollner J, Aronson NE, McHugh S, Nielson R, Hawkes C. Significant increases in serum cholesterol are seen among HIV patients taking protease inhibitors (abstract No. 12269). 12th World AIDS Conference, Geneva, 28 Jun - 3 Jul 1998.
13. Brundage RC, Fletcher CV, Fenton T, Fiske WD, *et al.* Efavirenz (EFV) and nelfinavir (NFV) pharmacokinetics (PK) in HIV-infected children under 2 years of age (abstract No. 719). 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 30 Jan - 2 Feb 2000.
14. Hayashi S, Wiznia A, Jaywardene A, *et al.* Nelfinavir pharmacokinetics in stable antiretroviral therapy experienced HIV infected children (abstract No. 427). 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 31 Jan - 4 Feb 1999.
15. Wiznia A, Stanley K, Krogstad P, Johnson G, for the PACTG 377 team. Combination nucleoside analogs plus nelfinavir, nevirapine, or ritonavir in stable antiretroviral therapy experienced HIV-infected children (abstract No. 697). 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2000.
16. Faye A, Compaggnucci A, Saidi Y, for the PENTA 7 Executive Committee (abstract No. 678). 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 4 - 8 Feb 2001.
17. Centers for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in pediatric practice. *MMWR* 1998; **47:** 1-43.