A Generalized Seizure Following Initiation of Nelfinavir in a Patient with Human Immunodeficiency Virus Type 1 Infection, Suspected due to Interaction between Nelfinavir and Phenytoin

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Nelfinavir, one of human immunodeficiency virus (HIV) specific protease inhibitors (PIs), is widely used for the treatment of HIV infection. Nelfinavir, which is metabolized with the cytochrome p450 isoforms, elevate the phenytoin level theoretically because nelfinavir acts as an inhibitor of phenytoin metabolism through the enzyme. However, we encountered a case of seizure recurrence caused by a lowered phenytoin level after initiation of nelfinavir. We should be aware of the change in the phenytoin level in concomitant use of nelfinavir.

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**Key words:** protease inhibitor, drug interaction, anticonvulsant, convulsion, cytochrome P450

**Introduction**

Human Immunodeficiency virus type 1 (HIV-1) specific protease inhibitors (PIs) dramatically improve the prognosis of HIV-1 infection (1-3). Four PIs, indinavir, saquinavir, ritonavir, and nelfinavir, are available in Japan in 1998 and used as key drugs in the combination therapy for HIV infection (4). Among them, nelfinavir is the most widely used PI because it is less toxic and easy to take compared with the other PIs (5,6). The liver enzyme, cytochrome P450 (CYP), is known to metabolize many kinds of drugs. Therefore, use of plural drugs metabolized by the enzyme sometimes causes unexpected side effects caused by drug-drug interactions. We report a case of suspected interaction between nelfinavir and phenytoin which resulted in lowered phenytoin levels and seizure recurrence.

**Case Report**

A 30-year-old Japanese homosexual male had the rupture of a right parietal arteriovenous malformation in 1981, resulting in mild left hemiparesis and left hemianopia. He was managed with Hydantol F®, which contains both phenytoin and phenobarbital in a tablet, for control of generalized tonic-clonic seizures. The last known seizure was 4 years prior to his current presentation. His anticonvulsant dosing was stable over the preceding three years. Stability of his phenobarbital level has suggested his good compliance even in variable levels of phenytoin throughout his clinical course (Table 1).

He was diagnosed as HIV positive in 1992 and was treated with zidovudine 300 mg twice a day beginning in 1993. Lamivudine 150 mg twice a day was added in 1996. The serum concentration of phenobarbital was 15.0 mg/l (therapeutic range; 10-40 mg/l) and phenytoin was 11.9 mg/l (therapeutic range; 10–20 mg/l in July 1997. His CD4 count was 85/µl and viral load was 12,000 copies/ml in August 1997. Because nelfinavir became available through an expanded program of the clinical study under Japan Tobacco Inc., the therapy was switched to a combination of nelfinavir 750 mg three times a day, didanosine 150 mg twice a day, and stavudine 30 mg twice a day on October 13, 1997. Didanosine was discontinued 4 days after initiation due to severe diarrhea. After 6 weeks of therapy, his CD4 count increased to 211/µl and viral load decreased to 2,100 copies/ml. He was taking antiretroviral agents regularly and his anticonvulsant dosing was not altered. The trough serum concentration of nelfinavir on November 10, 1997 and January 12, 1998 were 2,164.86 ng/ml and 2,997.63 ng/ml, respectively, which are within the normal expected value.

On January 3, 1998, he suddenly felt numbness in his left upper limb followed by a generalized tonic-clonic seizure. Electrolytes were within normal limits and serum glucose was 59 mg/dl. A computed tomography (CT) scan of the brain showed no interval change when compared to prior films. The seizure...
Table 1. Antiretroviral Agents and Serum Concentration of Anti-convulsants

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>Serum concentration (mg/l) of Phenytoin*</th>
<th>Serum concentration (mg/l) of Phenobarbital**</th>
<th>Antiretroviral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/91</td>
<td>9.7</td>
<td>18.0</td>
<td>None</td>
</tr>
<tr>
<td>2/95</td>
<td>21.6</td>
<td>19.0</td>
<td>AZT</td>
</tr>
<tr>
<td>7/97</td>
<td>11.9</td>
<td>15.0</td>
<td>AZT+3TC</td>
</tr>
<tr>
<td>11/97</td>
<td>5.0</td>
<td>13.7</td>
<td>NFV+d4T</td>
</tr>
<tr>
<td>12/97</td>
<td>5.2</td>
<td>14.4</td>
<td>NFV+d4T**</td>
</tr>
<tr>
<td>1/98</td>
<td>5.8</td>
<td>21.1</td>
<td>NFV+d4T***</td>
</tr>
</tbody>
</table>

*This patient has been taking 12 tablets/day of Hydantol F®, which contains 25 mg of phenytoin and 8.3 mg of phenobarbital per tablet, from 1991 through 1998. This resulted in 300 mg/day of phenytoin and approx. 100 mg/day of phenobarbital, respectively. **therapeutic range; 10–20 mg/l, ***therapeutic range; 10–40 mg/l, 'AZT: zidovudine, 3TC: lamivudine, d4T: stavudine, NFV: nelfinavir. "the 3rd week of the therapy, **the 6th week of the therapy, ***3 days after generalized seizure.

was controlled with 10 mg of diazepam and 100 mg of phenytoin. No sugar supplement was given, although the glucose level was slightly low. During hospitalization no further seizures occurred. An electroencephalography (EEG) revealed no epileptiform discharges. Lumber puncture was not performed because of the patient’s refusal. Past serum samples in stock were reviewed for anticonvulsant concentrations (Table 1). The results clearly disclosed that after the initiation of nelfinavir and stavudine, the serum concentration of phenytoin was remarkably decreased, which is suspected as the cause of his recurrent seizure.

Discussion

Protease inhibitors have remarkably improved the prognosis of HIV-infected patients in recent years. However, as with other protease inhibitors, nelfinavir is metabolized with CYP isoforms; primarily CYP3A followed by CYP2C19, CYP2D6, and possibly CYP2C9 (7). Therefore, drug-drug interactions remain a relevant issue, when combined drugs are also metabolized with these isoforms. On the other hand, phenytoin is metabolized with mainly CYP2C9 and CYP2C19 in part. Thus, the major interactions are associated with inhibition of CYP2C9 and the minor interactions are linked to CYP2C19 (8). Theoretically, concomitant use of the two may result in elevation of the phenytoin level because nelfinavir plays a role in phenytoin metabolism as an inhibitor of these isoforms. Actually, there is a report that suggests an increase in the serum phenytoin level with nelfinavir. A dose reduction of phenytoin could be considered when used together. However, in this case, nelfinavir might act as an inducer of CYP. In fact, some PIs are reported to act as the inducer for several weeks after starting the PI, although there is no evidence to support this speculation in this case.

Reviewing the given results, the synchronicity of initiation of nelfinavir and the decrease in the serum phenytoin level strongly suggest that nelfinavir reduces the serum phenytoin levels. Although we cannot exclude the possibility that zidovudine interfered with the phenytoin level (9) or that the concomitant use of stavudine may have contributed to the reduced phenytoin level, there are few reports to support these theories (10). The glucose level was low (59 mg/dl) at the seizure. However, it was controlled without glucose administration, indicating that the low level of glucose was not the cause of his generalized tonic-clonic seizure. Before starting nelfinavir on November 1997, he was taking 12 tablets/day of Hydantol F® regularly for 6 years. During this period, the serum concentration of both phenytoin and phenobarbital was stable. Therefore, there is slight possibility that the Long-term use of phenobarbital influenced the phenytoin metabolism. In either case, we should be well aware of the change in the phenytoin level in concomitant use of nelfinavir. This information is very important especially for Japanese hemophiliacs with HIV infection, because some of them are taking anticonvulsants for prophylaxis of convulsion as sequelae of intracranial hemorrhage during childhood.

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References