Commentary

Continuing HIV therapy in the ICU

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Abstract

The risks and benefits of stopping antiretroviral therapy in patients admitted to the ICU are largely unmeasured. In many cases therapy has to be stopped, as parenteral preparations are unavailable for all but one of the antiretroviral agents. Stopping treatment suddenly may be associated with increased risk of resistance because of the long half-life of some of the drugs, and also the risk of increased immunosuppression due to the viral load rebounding. Drugs given through the enteral route may be poorly absorbed, which again may lead to drug resistance. By inhibiting cytochrome P450 3A4 the drugs interfere with the metabolism of many other compounds routinely used in the ICU. Furthermore, the drugs themselves are occasionally associated with severe toxicity such as pancreatitis and lactic acidosis, which can have devastating consequences. Much active research in all of these areas is now needed.

Keywords drugs, HAART, HIV, ICU, pharmacokinetics

The widespread introduction of highly active antiretroviral therapy (HAART) in 1996 has revolutionised the prognosis of HIV disease [1–3]. The incidence of death from AIDS has fallen markedly and many opportunistic infections have become relatively rare. Consequently, the pattern of referrals to the intensive care unit (ICU) has altered. It is important to appreciate, however, that in spite of advances in treatment, 30% of new HIV diagnoses are made when patients are already severely immunocompromised; the patient may be presenting with AIDS for the first time [4]. A dilemma arises when a patient on HAART is admitted to the ICU. Unless the admission is directly related to HAART, there is little consensus on what to do in terms of continuing treatment.

HAART enables the immune system to function relatively normally and has demonstrable benefit in at least two areas impinging on ICU. Viral load is suppressed in patients on haemodialysis, and morbidity and mortality is considerably reduced [5]. Similarly the incidence of both community- and hospital-acquired pneumonia is reduced in patients on HAART [6]. There are little data showing how HAART patients respond to treatment of nonHIV related conditions. However, the impact on immunity, the reduction in morbidity from dialysis, and the reduction in pneumonia are all circumstantial evidence that patients on HAART are more resilient and therefore potentially more responsive, at least to infective problems.

The second group of patients with HIV may have developed resistance to some or all of their antiretroviral therapy. These patients continue to have poorly controlled viral replication, and are at risk of opportunistic infection as their immune suppression continues.

The third group of patients with HIV may have an acute illness that is immunosuppressive in nature. If HAART is discontinued on admission to ICU, the risk of further opportunistic infections for these patients will increase dramatically [7].

The fourth and final group may be presenting with complications directly related to their antiretroviral therapy, such as lactic acidosis and pancreatitis [8,9]. Nucleoside analogues such as zidovudine or stavudine have been associated with the development of mitochondrial dysfunction [10,11]. The drugs can inhibit mitochondrial DNA polymerase gamma, causing abnormalities in the respiratory chain and life-threatening lactic acidosis. Pancreatitis may be

HAART = highly active antiretroviral therapy; ICU = intensive care unit.

part of this syndrome but is also related to the use of specific antiretroviral drugs, such as didanosine. Some protease inhibitors may cause large increases in cholesterol, triglycerides, and glucose, which can lead to severe acute metabolic complications.

Non-nucleosides, such as Nevaripine, have been associated with hepatic failure. Other, more rare, syndromes, such as uncontrolled fits in neonates and severe hypotension, have been reported with other HIV drugs. Liver toxicity is a major concern with HAART, in its own right and in combination with certain other agents used in ICU, especially in patients with chronic viral hepatitis.

Resistance, absorption, and interactions

The critically ill patient on antiretroviral drugs is a challenge. Much of what is done is based on physician experience rather than data from controlled studies. Clearly, if the presenting condition is related to the HIV therapy, the drugs must be stopped. It is often difficult to substitute with alternative regimes because of overlapping toxicities, previous drug resistance, or difficulties in administrating the drug. When patients are nil by mouth abruptly stopping antiretroviral therapy may cause a sudden fall in CD4+ cell count and a rise in viral load. Some patients may even develop an acute seroconversation illness. Interestingly, however, stopping and starting HAART is a strategy used for trying to enhance immune responses to HIV in asymptomatic patients [12].

Discontinuing some drugs, such as the non-nucleosides, may even lead to drug resistance. Once they are stopped, some drugs exist in the plasma and cells for several days at sub-therapeutic levels because their half-lives are 3–5 days. Once the drugs are discontinued, the virus replicates and re-emerges in the plasma. This may enable the virus to develop resistance to the drug.

Resistance may also occur because of poor drug absorption. If plasma and cellular levels of some of the compounds are not adequate then resistance can occur after relatively few doses of the non-nucleosides or lamivudine.

Unfortunately, most antiretroviral drugs can only be given in patients with a normally functioning gut and who can be fed orally or through a nasogastric tube. Zidovudine is the only drug that can be given intravenously. There are few data on the absorption and pharmacokinetics of any of the antiretrovirals when given through a gastric or jejunal feeding tube. Drug levels can be measured for protease inhibitors [13] and non-nucleosides but plasma levels are not reliable for nucleosides, which are activated by intracellular phosphorylation.

Drug interactions are important, especially when enzymes inducers, such as phenytoin and rifampicin, are used. There are still relatively few data on the interactions between many of the drugs used in the ICU and those used in HIV therapy. The protease inhibitors and the non-nucleosides can act as cytochrome P450 3A4 inhibitors, and affect the metabolism of many of the drugs used in ICU, such as midazolam or opiates.

In practical terms it makes sense to continue HIV treatment where possible. The consequences of stopping treatment may be serious, and research is needed on drug absorption and stopping-and-starting therapy in the ICU, as well as drug interactions. The effect of HAART on ICU outcomes, either directly or indirectly through its effect on viral load and CD4+ cells, needs to be explored.

Competing interests

None declared.

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