LETTER TO EDITOR

Stavudine delivery in an extended release formulation: Will it provide the right *in vivo* pharmacokinetics — Some key observations

Sir,

Saravanakumar *et al*, (2010) have performed an extensive study to enable the delivery of stavudine in a once daily extended release formulation.[1] The *in vitro* evaluation has been performed with multiple formulation options to enable the selection of the right formulation system that renders once-a-day delivery of stavudine, ensuring that zero order release is maintained during the entire duration. As evidenced by the generated data, the recommended formulation (F9), appears to release approximately 4% of the drug load every hour leading to a complete release of the stavudine drug load by 24 hours.

The authors argue that there is a need for the ER formulation of stavudine to improve patient compliance and also limit the frequency of dosing. Also, as is to be expected, one may have a better control of the plasma / serum concentrations if dosed in ER formulation, and thus, it may improve the safety profile of the compound.

Although it is true that the frequency of dosing of stavudine is twice daily, there appears to be no major issue of compliance noted in the therapy. Hence the need of an ER formulation, although not necessary for stavudine, may help in providing choices for patients if they so desire. However, before one embarks on a formulation strategy, some fundamental checks / balances need to be made in an unbiased manner, prior to committing resources on generating such experimental data.

The intent of this note is to review some key aspects of the pharmacokinetics and disposition of stavudine in light of the proposed once daily ER formulation strategy,[1] and to provide a balanced view of such formulation strategies, which has not appeared to consider some fundamental pharmacokinetic behaviors of the compound in question.

In arecently published human ^{14}C study, stavudine is reported to be rapidly and completely absorbed in humans.[2] The unchanged drug, accounting to approximately 61% of the administered dose, was accounted for in the urine, with a small percentage of radioactivity in the fecal samples, suggesting the predominant role of the renal elimination pathway for its excretion. As urine accounted for almost the entire administered radioactive dose of stavudine, no gastrointestinal absorption issues were cited for this drug.[2] The half life value of 2.35 hours suggested the need for a second daily dose of stavudine, to maintain the needed plasma / serum threshold concentrations, to elicit its pharmacodynamic response.[2] No data are available in literature pertaining to the likely absorption sites of stavudine after oral administration, although all published pharmacokinetic data, including the ^{14}C oral dose data, strongly suggest that the absorption of stavudine is likely to happen in the upper gastrointestinal tract itself.[2-4]

However, there has been a suggestion that stavudine may be subject to carrier-mediated absorption in the preclinical model.[5] Even as the relevance of such preclinical work to human subjects is not clearly understood, such data appear to be inconsequential,[5] as stavudine has excellent permeability and poses no challenges for passive absorption across a wide dose range, in human subjects. In another interesting study, performed using *in-situ* intestinal preparations, it has been found that among the three anti-viral agents, azidothymidine (AZT), stavudine, and didanosine, the colonic absorption favored AZT much more than stavudine.[6] Even as stavudine absorption in other intestinal segments such as the duodenum and jejunum was comparable to AZT; didanosine was least absorbed in any of the intestinal segments, owing to its inherent stability issues.[6]

In the absence of intestinal absorption data for the entire gastrointestinal tract, it is kind of tricky to develop an ER formulation of stavudine, which is expected to deliver the dose throughout all segments to facilitate timely absorption of the drug. Such *in vivo* absorption data (development of *in vitro–in vivo* correlation {IVIVC}) may be vital in the design of the ER formulation, especially for the selection of appropriate polymers and / or excipients that govern the release of the drug, based on the local environment requirements.[7,8] Nevertheless, the developed ER formulation of stavudine, based on zero order release kinetics, should produce plasma levels that maintain the required threshold levels of stavudine without compromising its anti-viral properties. As an ER formulation is not expected to match the immediate release (IR) product

in its rate of absorption, the development and registration of an ER product would not be based on a regular bioavailability / bioequivalence strategy, but rather on the full dossier of establishment of safety and efficacy of the drug product in the relevant clinical population.[9] The key question would be: is it the right strategy for developing the new ER product of stavudine?

Although it is important to be innovative in our approaches to establish newer formulation options, one has to be pragmatic. For instance, in the field of treating HIV infection, today's medicinal arsenal depends on a combination (double or triple drug combination), and hence, an ER formulation of one agent may provide a limited option. More importantly, unlike IR formulations, ER formulations may provide no flexibility in dosage adjustments (on weight basis), which may be required in fragile HIV-infected patients. With special reference to stavudine, there needs to be an age-related dosage adjustment until adulthood,[10] and an ER formulation may not provide the flexibility for any dosage adjustments.

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