PHARMACOKINETIC STUDY OF ORAL FUSIDIC ACID (FORMULATION: FILM-COATED TABLET) AFTER THE FIRST DOSE AND REPEATED DOSES IN ELDERLY SUBJECTS

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SUMMARY

The frequency and severity of infectious disease, particularly staphylococcal diseases, increase with age. Ageing is also responsible for a variation in a large number of physiological parameters, which themselves are likely to modify the pharmacokinetic properties of a large number of medicinal products.

The pharmacokinetics of fusidic acid (FA), which has established anti-staphylococcal efficacy, is well-known in healthy volunteers, although there is insufficient data for elderly subjects. It therefore seemed necessary to study its pharmacokinetics after the first dose and repeated doses in subjects over the age of 65, in its oral form (film-coated tablets of 250 mg sodium fusidate) the one most likely to result in pharmacokinetic changes, and at a dose of 1 g a day in two doses, the most common dosage used.

6 men and 6 women, with a median age of 81 (75-95) and weighing 54 kg (40-95) were included in this study. The prescribing of oral fusidic acid was justified in all cases by a considerable skin superinfection. In all cases, the patients also presented with a disease in addition to the existing infection (mainly cardiovascular) with their related treatments (average ratio of the number of treatments combined with FA: 2). The laboratory results, although abnormal in 58% of cases, was within the protocol standards (transaminases ≤ 3 times, total bilirubin and alkaline phosphatases ≤ 2 times the normal upper value; creatinine < 220 µmol/l). The treatment lasted a minimum of 5 and a half days. A case of nausea was recorded but did not require that the treatment be stopped.

Samples were taken from patients fasting before the first dose (0 hours), then at 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 12 hours (phase I); before and after the morning dose on day 5; and at the time of the last dose (while still fasting), with a sampling sequence identical to that in phase I and a further 3 samples taken 24, 36 and 48 hours after the dose.

Tests were then carried out by LEO in Denmark (H. SORENSEN) using the HPLC method and the pharmacokinetic analysis of the results by Professor’s team at Hôpital de Bicêtre.

The maximum concentration (Cmax) after the first dose of 500 mg was 32.6 ± 8.1 mg/l and the corresponding Tmax 2.5 ± 1.1 hours. After repeated doses, the peak concentrations increased significantly: 119 ± 34.7 mg/l, with no significant change in Tmax. The reduced total clearance was significant (factor 3) and the accumulation ratio significantly higher than the theoretical ratio (factor 3).

Several comments can be made and conclusions drawn from this study:

There were variations between the first dose and repeated doses, but these were not specific to elderly subjects. Even if they seemed to be a little more marked amongst the latter group, they are observed in a healthy volunteer in IV form and demonstrate a saturation of hepatic metabolism.

The dosing schedule of 4 tablets of sodium fusidate (1 g) a day was therefore validated and, except in exceptionally severe cases, a higher dosage did not appear to be justified.

In fact, on the one hand, the same steady-state serum concentrations were achieved at 80 to 120 mg/l as 3 daily infusions (1.5 g) in healthy volunteers, a dosage administered in the case of a severe staphylococcal infection. On the other, it has proven successful for a number of years in the treatment of moderate staphylococcal infections.

The similarity in pharmacokinetic results in a young subject in the same conditions demonstrates that age only has a minor effect on the pharmacokinetics of oral FA and that the same dosing schedule can be used for elderly subjects.

A new dosage reduction to less than 4 tablets a day may be considered, depending on the serum concentrations with respect to the FA MIC vis à vis the staphylococci. If approved, it may, in the light of this study, be applied to the whole adult population regardless of age.