Plasma Concentrations and Comparative Bioavailability of Bemetizide and Triamterene in Combination

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Introduction

Thiazide diuretics such as bemetizide (Fig. 1) and the potassium-sparing triamterene (Fig. 1) have been in clinical use for several years but it is only recently that pharmacokinetic data on these compounds have become available. A major reason for this is the increasing awareness of the usefulness of pharmacokinetic data and of the availability of adequately sensitive and specific methods for the measurement of these drugs in biological fluids.

Measurement of Bemetizide and Triamterene

Both bemetizide and triamterene can be measured by reversed-phase high-performance liquid chromatography (HPLC) using an ultraviolet absorption detector for the former (Brodie et al. 1978) and a fluorescence detector for the latter (Brodie et al. 1979).

Some details of the analytical methods for both drugs are shown in Tables 1 and 2 respectively.

Fig. 1. Structure of bemetizide 1 and triamterene 2

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Table 1. Characteristics of the HPLC methods for the measurement of bemetizide in plasma and urine

<table>
<thead>
<tr>
<th>Internal standard</th>
<th>Cyclopenthiazide</th>
<th>Detector</th>
<th>Ultraviolet absorption at λ 271 nm</th>
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</table>
| Sensitivity       |                  | Precision| Plasma - 10 ng/ml plasma ± 15% at 25 ng/ml  
                  |                  |          | ± 3% at 75 ng/ml  
                  |                  |          | ± 5% at 200 ng/ml  
                  |                  |          | ± 4% at 600 ng/ml  
| Recovery          | Plasma - mean 90% 
                  |          | Urine - mean 98% |

Table 2. Characteristics of the HPLC methods for the measurement of triamterene in plasma and urine

| Internal standard | p-Methoxytriamterene | Detector | Fluorescence, excitation λ 365 nm  
                  |                    | emission λ 440 nm |
|-------------------|---------------------|----------|-----------------------------------|
| Sensitivity       |                     | Precision| Plasma - 1 ng/ml plasma ± 11% at 1 ng/ml  
                  |                     |          | ± 3% at 20 ng/ml  
                  |                     |          | ± 6% at 200 ng/ml  
                  |                     |          | ± 4% at 400 ng/ml  
| Recovery          | Plasma - mean 79%  
                  |          | Urine - mean 85% |

Concentrations of Bemetizide in Plasma

Concentrations of bemetizide have been determined in human plasma after administration of the drug alone and in combination with other drugs.

After single oral doses of 25 mg of bemetizide alone, peak mean drug concentrations in plasma of 83 ng/ml were reached at 3–4 h (Fig. 2). Thereafter mean plasma concentrations declined to 15 ng/ml as an apparent first order process with a half-life of approximately 7.5 h. After 24 h, mean plasma concentrations of bemetizide were below the limits of detection (< 10 ng/ml). Peak concentrations in different subjects varied less than 2-fold, ranging between 69–108 ng/ml and occurring between 2 and 6 h (Table 3).

After single oral doses of 25 mg of bemetizide in combination with 50 mg of triamterene, peak mean drug concentrations in plasma of 66 ng/ml were reached at 4 h (Fig. 2). Thereafter mean plasma concentrations declined to 21 ng/ml at 16 h after dosing as an apparent first order process with an approximate half-life of 7.5 h. After 16 h, mean plasma concentrations of bemetizide were below the limits of detection (< 10 ng/ml). Peak concentrations in different subjects varied about 2-fold, ranging between 46–107 ng/ml and occurring between 3 and 8 h (Table 3).

The rate of absorption of bemetizide was not significantly altered when the drug was ingested together with triamterene (Table 3 and Fig. 2). However, comparison of the areas under the plasma concentration-time curves (Fig. 2) showed that the extent of bioavailability of bemetizide in these studies was significantly (p < 0.01) less when the drug was administered together with triamterene (Table 4) than when it was administered alone. An explanation for this difference is that the diuretic action of triamterene enhanced the plasma clearance of bemetizide; however, this was not indicated by an increase in the amount of unchanged drug excreted in the urine (see Table 5). Also, formulation effects seem an unlikely explanation since the dissolution rates of the two formulations were rather similar.

The clinical significance of this finding (Tables 3 and 4) is debatable since the reverse result was obtained in another study when mean plasma concentrations were greater after bemetizide (20 mg) was administered in combination with triamterene (40 mg), dihydralazine (40 mg) and bupranolol (40 mg) than when it was ad-