Stability and Pharmacokinetics of m-[131I]iodobenzylguanidine in Patients

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ABSTRACT

A pharmacokinetic study was done to elucidate the body distribution, elimination, and metabolism of m-[131I]iodobenzylguanidine (m-[131I]IBG). For this purpose, an analytical method using solid phase extraction columns was developed. m-[131I]IBG was administered as an i.v. infusion according to certain schedules with doses of 7,055 to 13,580 MBq/m². At the start of the infusion m-[131I]IBG accounted for 93.0 ± 2.3% (SD; n = 10) of the total radioactivity. At the end of the infusion m-[131I]IBG accounted for 88.0 ± 7.4%. The non-m-IBG-bound radioactivity was predominantly 131I.

The pharmacokinetic parameters (n = 7) are adequately described by a three compartment model. The parameters for m-[131I]IBG were determined with a mean terminal half-life of 37.0 h, a volume of distribution of 307 liters/m², and an area under the curve value of 1091 kBq x h/ml. The total body clearance was 189 ml/min/m². The values for I3II showed a terminal half-life of 71.6 h, a volume of distribution of 190 liters/m², and an area under the curve value of 1537 kBq x h/ml. The total body clearance was 70 ml/min/m².

The selectivity of the m-[131I]IBG treatment might be improved by a reduction of 131I in the infusion fluid and further investigations are warranted.

INTRODUCTION

m-[131I]IBG, a guanethidine derivative, is selectively concentrated by sympathetic nerve tissue (1-4). 131I- and 123I-labeled material is used for scintigraphy of the adrenal medulla, pheochromocytomas, and neuroblastomas (5-9). In in vitro studies Buck et al. (10) showed that m-[131I]IBG was actively concentrated in neuroblastoma cell lines resulting in cell death. m-[131I]IBG was then used in the treatment of disseminated neuroblastoma and its efficacy was noted by several authors (11-13).

A pharmacokinetic study was done to elucidate the body distribution, elimination, and metabolism of m-[131I]IBG and is the subject of the present report.

MATERIALS AND METHODS

Five patients (7 treatment courses) with neuroblastoma stage IV prior to chemotherapy were enrolled in this study. The age range was 3 to 9 years (median, 3 years). All patients had normal renal and liver function as assessed by creatinine, blood urea nitrogen, bilirubin, albumin, and coagulation profile. m-[131I]IBG was then administered at doses of 7,055 to 13,580 MBq/m² (1 MBq = 27.027 µCi) as an i.v. infusion as repeated on day 2 in patients with treatment on 2 consecutive days and on subsequent days. The samples were kept at 4°C until measurement.

Spontaneously voided urine was collected in 24-h samples. All samples were kept at room temperature until analyzed.

Prior checks indicated that both plasma and urine samples from patients are stable for more than 8 days under these conditions. Nonetheless all measurements were carried out within 48 h.

m-[131I]IBG for clinical use was supplied by Amersham-Buchler, Braunschweig, Federal Republic of Germany. m-[131I]IBG was shipped frozen on dry ice. After thawing it was diluted with 0.9% NaCl solution prior to administration.

Plasma and urine samples were separated by use of a solid phase extraction technique on a Vac-Elut system (ICT, Frankfurt, Federal Republic of Germany) equipped with Baker C18 columns (1 ml) (J. T. Baker, Groß-Gerau, Federal Republic of Germany). The columns were activated by washing with 5 ml methanol (Uvasol, Merck, Darmstadt, Federal Republic of Germany) followed by 10 ml of double distilled water.

One hundred µl plasma or urine were applied directly to the Baker columns. 131I was eluted with 2 ml of water. The columns were then washed with a further 10 ml of water. The remaining m-[131I]IBG was then eluted with 1 ml of methanol-sodium dihydrogen phosphate (0.1 M) 80:20 (v/v) into plastic vials. The eluates were counted in a Berthold LB MAG 510 gamma counter (Berthold, Wildbad, Federal Republic of Germany).

The quality of the solid phase extraction technique was checked by an HPLC method. The chromatographic system consisted of a Waters M-45 solvent delivery system and a Waters Model U6K injector. Separation was obtained with a Waters Associates C18Bondapak column (30 cm x 3.9 mm inside diameter; 10-µm particle size). Chromatographic Conditions. All reagents used for chromatography were HPLC grade. The optimum isocratic system for the resolution of m-[131I]IBG, 131I, and degradation products was found to consist of methanol-water (35:65, v/v) containing 0.1 m sodium dihydrogen phosphate. The flow rate was maintained at 0.9 ml/min.

Urine was injected without sample clean up, and 150 µl methanol were added to 50 µl plasma and centrifuged after 2 min at 3000 x g; 50 µl of the supernatant were injected into the HPLC system.

Samples after HPLC were collected at 1-min intervals and counted in a Berthold LB MAG 510 gamma counter.

Computation of Results. Nonlinear least-squares regression analysis of data was performed with the TOPFIT program (14, 15), and curve fitting was accomplished with a data weighting of (C_{observed} - C_{calculated})²/C_{observed} for plasma and (C_{observed} - C_{calculated})² for urine.

RESULTS

The reproducibility of the separation of m-[131I]IBG from 131I at an activity of 500 Bq/ml, which was the lowest concentration measured in clinical samples, was determined by analyzing a newly manufactured batch by the solid phase extraction technique ten times; 95.27 ± 1.58% (SD) consisted of m-[131I]IBG and 2.30 ± 0.18% of 131I. The HPLC analyses of the infusion fluid also showed that more than 98% of the radioactivity was m-[131I]IBG and 131I. A typical measurement of 1-min samples of the HPLC eluate is given in Fig. 1.

The coefficients of correlation of the HPLC method and the
solid phase extraction technique for m-[131I]IBG and 131I in plasma and urine samples were all greater than 0.94. These data allowed us to measure the clinical samples by use of the solid phase extraction technique. At the start of the infusion, m-[131I]IBG accounted for 93.0 ± 2.3% (n = 10) of the total radioactivity. At the end of the infusion m-[131I]IBG accounted for 88.0 ± 7.4%. The non-m-[131I]IBG radioactivity was predominantly 131I. The data for all doses are given in Table 2.

The amounts of m-[131I]IBG and 131I excreted in urine are expressed as a percentage of dose in Table 3. In urine and plasma samples, more than 98% of the radioactivity was m-[131I]IBG and 131I after m-[131I]IBG treatment.

The pharmacokinetic parameters were estimated using both urinary and plasma values for 7 treatment courses of 5 patients. The combined data were best described by an open three compartment model. The results of the pharmacokinetic analyses for m-[131I]IBG and 131I are listed in Tables 4 and 5, respectively.

The plasma disappearance curve and urinary excretion of 131I are shown in Fig. 2. The plasma disappearance curve and urinary excretion of m-[131I]IBG in patient I. H., cycle 5, are shown in Fig. 3. The efficacy and side effects of m-[131I]IBG in neuroblastoma have been previously reported (11, 12).

**DISCUSSION**

The efficacy and side effects of m-[131I]IBG in neuroblastoma have been previously reported (11, 12).
STABILITY AND PHARMACOKINETICS OF m-[131I]IBG

The analytical technique of using a solid phase extraction method described in this report permitted us to measure m-[131I]IBG and 131I in plasma, urine, and infusion fluid rapidly and with high sensitivity.

The analyses of the infusion fluid showed that immediately after shipment only 93.0 ± 2.3% of the total radioactivity is bound to mIBG and that this binding was unstable over time. The percentage of free 131I increased to 10.3 ± 6.9% at the end of the infusion. Due to the longer terminal half-life of 131I only 93.0 ± 2.3% of the total radioactivity is accumulated in adrenal tissue, neuroblastoma, and within liver and spleen. These results suggest a deep tissue compartment. The large mean value of the volume of distribution (307 liters/m²) suggests that much of m-[131I] IBG is sequestered in tissue and slowly released.

The disappearance of m-[131I]IBG and 131I from plasma is adequately described by a three compartment open model with a terminal half-life of 37.0 and 71.6 h, respectively. These first pharmacokinetic data on m-[131I]IBG show that the treatment of neuroblastoma with m-[131I]IBG may be improved by purification and stabilization of the drug. This may be achieved by addition of stabilizing compounds, “bedside purification” by solid phase separation techniques, or precipitation of 131I as iodide prior to application. Alternatively, as suggested by our observation that chemoradioysis of m-[131I] IBG was not observed in plasma, the stability of m-[131I]IBG may be better in buffered protein solutions.

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