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Short communication

Renal effects of S10036 in man

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Summary. The renal hemodynamic and tubular effects of S10036 (fotemustine) were evaluated in seven patients with advanced malignancy. Initial evaluation carried out prior to treatment and repeated 1 day after the first fotemustine infusion and 7 days after the second included clinical, haematological parameters, liver-function tests, and determination of the glomerular filtration rate, renal blood flow and enzymuria. The glomerular filtration rate was 108 ± 3.7 ml/min before treatment and remained stable after the first (117 ± 5 ml/min) and second (124 ± 6 ml/min) fotemustine infusions. Renal blood flow and urinary β_2-microglobulin and *N*'-acetylglucosaminidase excretion were also not modified by fotemustine administration. We conclude that fotemustine does not acutely alter renal haemodynamics, nor does it have direct tubular toxicity.

Introduction

Nitrosoureas are lipid-soluble agents that have demonstrated clinical activity against malignant melanoma, brain tumors and malignant lymphomas [2, 5, 10]. Because of the ease of administration of these agents, their ability to cross the blood-brain barrier, their high lipid solubility and their broad spectrum of anti-tumor activity, they have the potential for widespread use either alone or in combination with other oncolytic agents; however, their nephrotoxicity has been a factor limiting such widespread use.

The mechanism of nitrosourea nephrotoxicity remains unknown. In most patients renal failure occurs insidiously, with the initial evidence of renal insufficiency occurring 1–6 years after the onset of therapy [4, 9]. However, some have been observed to develop an increase in serum creatinine concentrations while receiving nitrosoureas and later progressed to renal failure [6]. Marked glomerular sclerosis, interstitial fibrosis and extensive tubular atrophy have been observed both in humans and in experimental animals [9]. Other drugs, such as cyclosporine, may lead to the same histopathological damages, and it has been suggested that renal vasoconstriction and/or direct tubular cell toxicity may be involved in these alterations [7, 8]. Therefore, this study was designed to assess the haemodynamic modifications and/or direct tubular toxicity induced by S10036 (fotemustine), a new nitrosourea.

The renal haemodynamic and tubular effects of fotemustine were evaluated in seven patients. The glomerular filtration rate (GFR) was measured by inulin clearance and the effective renal plasma flow (ERPF), by the renal clearance of *p*-aminohippuric acid (PAH). The renal plasma flow (RPF) was deduced from the renal blood flow (RBF) and haematocrit. Tubular toxicity was assessed according to modifications in urinary β_2-microglobulin and *N*'-acetylglucosaminidase (NAG) excretion.

Patients and methods

Our patient population consisted of seven patients with advanced malignancy who were evaluated before and after two infusions of fotemustine (100 mg/m^2) that were performed with a 7-day interval. The clinical characteristics of these patients are outlined in Table 1. Subjects had received one or more cancer chemotherapy agents to which their disease had proved resistant. Initial evaluation carried out prior to treatment and repeated 1 day after the first fotemustine infusion and 7 days after the second included clinical haematological parameters, liver-function tests, and determination of the glomerular filtration rate, renal plasma flow and enzymuria. Fotemustine was given at a dose of 100 mg/m^2 over 1 h as an i.v. infusion in 5% glucose solution. For determination of inulin and PAH clearance, patients underwent i.v. hydration with 2 l 5 isotonic saline. A priming dose of inulin (50 mg/kg) and PAH (5 mg/kg) was followed by a continuous infusion of these substances, which was calculated to maintain brisk diuresis and a nearly stable plasma concentration of inulin and PAH. After a 60-min equilibration period, three carefully timed urine collections were performed, and plasma and PAH levels were assessed at the beginning and the end of each collection interval. The average of three determinations of inulin and PAH clearance represented the values for glomerular filtration rate and effective renal plasma

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Table 1. Patients' characteristics

Patient number	Age	Sex	Diagnosis
1	65	M	Melanoma
2	47	F	Pancreatic carcinoma
3	38	M	Melanoma
4	53	M	Adenocarcinoma
5	67	M	Renal malignant carcinoid tumor
6	50	M	Renal malignant carcinoid tumor
7	38	F	Melanoma

Table 2. Effects of fotemusine on the glomerular filtration rate, renal plasma flow, and urinary β_2-microglobulin and NAG excretion

	GFR (ml/min)	ERPF (ml/min)	β_2 Microglobulin (mg/l)	NAG (nmol/h mg CR)
Before treatment	108±4	418±44	0.08±0.04	208±42
A	117±5	394±33	0.04±0.008	220±3
B	124±6	392±37	0.02±0.004	240±93

A, 1 day after the first fotemustine infusion; B, 7 days after the second infusion; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; NAG, *N*'-acetylglucosaminidase; CR, creatinine

flow, respectively. β_2-Microglobulin and NAG were measured by radioimmunoassay and enzymatic assay, respectively.

Statistical analysis. Statistical analysis were performed on an IBM PC using the number-cruncher statistical system (Kayville, Utah). The results are reported as the mean ±SEM; the Wilcoxon test was used to compare means. The criterion of significance was $P < 0.05$.

Results

Clinical tolerance was good except for nausea. There was no modification in either haematological or liver functions. The GFR was 108±3.7 ml/min before treatment and remained stable after the first (117±5 ml/min) and second (124±6 ml/min) fotemustine infusions (Table 2). The effective renal plasma flow was not modified by fotemustine infusion (418±44 ml/min before treatment vs 394±33 ml/min and 392±37 ml/min after drug infusion; Table 2). Urinary β_2-microglobulin and NAG excretion remained within the normal range after fotemustine administration (Table 2).

Discussion

S10036 is a new nitrosourea that has demonstrated clinical activity against malignant melanoma, brain tumor and hematosarcoma [10]. The present study was designed to evaluate the acute renal tolerance of this drug.

In this study, fotemustine did not induce nephrotoxicity. Inulin and PAH clearance, which reflect GFR and ERPF, were not altered either 1 day or 7 days after fotemustine infusion. Drug-induced tubular toxicity can be quantitated by monitoring urimary markers for tubular cell damage. Two widely used markers are urinary NAG [3] and β_2-microglobulin [1]. β_2-Microglobulin is a small protein that is freely filtered at the glomerulus and nearly reabsorbed in the proximal tubule, whereas NAG is a tubular enzyme. After damage to tubular cells, the urinary levels of these enzymes increase. Urinary β_2-microglobulin and NAG excretion were not modified by fotemustine, indicating the absence of direct tubular toxicity. In conclusion, fotemustine does not modify renal haemodynamics, nor does it alter enzymuria. Further studies are being conducted to evaluate the long-term renal tolerance of this drug.

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