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Report

A Retrospective Analysis of Fenoldopam Renal Excretion in 65 Subjects: Evidence for Possible Intrarenal Formation of Fenoldopam from Its Metabolites

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Clinical studies have suggested that the dopamine DA_1 agonist, fenoldopam, may exhibit nonlinear renal excretion in humans. A retrospective population pharmacokinetic analysis of the renal excretion of fenoldopam and one of its major metabolites, fenoldopam-8-sulfate, was conducted in 65 healthy volunteers to examine this phenomenon. Fenoldopam-8-sulfate exhibited a mean (±SE) renal plasma clearance of 129 ± 4 ml/min, which was independent of its AUC. In contrast, fenoldopam renal plasma clearance ranged from 2220 to 150 ml/min and decreased nonlinearily with increasing fenoldopam AUC. Fenoldopam renal clearance was characterized as a function of fenoldopam AUC using a nonlinear saturation model. The analysis predicted an initial maximal renal clearance of 2852 ml/min, which decreased to 78 ml/min at maximal inhibition. The fenoldopam AUC required to half-saturate fenoldopam renal clearance was 5.2 ng × hr/ml. The elevated clearance values for fenoldopam, beyond normal physiologic limits for renal blood flow in man, suggest that intrarenal formation of fenoldopam from one or more of its circulating metabolites may be contributing to the observed nonlinear decreases in fenoldopam renal excretion. Preliminary data from our laboratory suggest that *in vivo* desulfation of fenoldopam-8-sulfate to fenoldopam does occur in the dog.

KEY WORDS: fenoldopam; renal excretion; reversible metabolism; pharmacokinetics.

INTRODUCTION

Fenoldopam is a potent peripheral dopamine agonist which has shown beneficial hemodynamic effects including increases in renal plasma flow and reductions in blood pressure following intravenous or oral administration (1–3). At low intravenous infusion rates (0.05–0.1 μg/kg/min) fenoldopam increases renal blood flow in animals and man by 50 to 70% (4,5). The compound is extensively metabolized to a variety of sulfate, glucuronide, and methyl conjugates on the catechol portion of the molecule, accounting for 40% of an orally administered dose. Fenoldopam renal clearance in man is several fold greater than the glomerular filtration rate, indicative of net tubular secretion; however, due to extensive presystemic and systemic metabolism, less than 1% of an orally administered dose is recovered in the urine as unchanged fenoldopam, which represents 10–15% of the total fenoldopam clearance (6). Recently, coadministration of acetaminophen acutely (1000 mg) or chronically (1000 mg TID × 7 days) has been shown to decrease fenoldopam renal clearance in man (6). A direct competitive effect of acetaminophen on fenoldopam renal transport is unlikely considering the presumed specificity of fenoldopam for cationic transport systems (7) and the lack of experimental data demonstrating that acetaminophen itself undergoes active tubular secretion (8). Furthermore, single-oral dose ranging experiments with fenoldopam alone, performed in man, confirm fenoldopam's renal clearance changes observed previously in the presence of acetaminophen (9), and fenoldopam renal clearance was found to decrease with increasing oral dosages of fenoldopam. Nonlinear increases in fenoldopam AUC were also noted, accompanied by saturable first-pass formation of a variety of metabolites including both sulfated metabolites.

These observed changes in renal clearance may be related to increased plasma concentrations of fenoldopam, resulting from either acetaminophen-induced changes in fenoldopam presystemic metabolism or, in the case of the dose ranging experiments, through oral dosing adjustments. These elevated plasma concentrations may approach the capacity of the kidney to secrete fenoldopam. If this explanation is correct, fenoldopam possesses an unusually high affinity for the transport mechanisms involved, considering the low levels of fenoldopam routinely observed in plasma (0.1 to 50 ng/ml). Alternatively, a secondary renal mechanism, other than tubular secretion, may be involved.

Considering the limited data available and the fact that renal elimination is a minor excretory route for fenoldopam, a more extensive verification of this phenomenon was

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sought in order (i) to confirm that fenoldopam renal clearance is saturable and (ii) to assess its clinical impact.

METHODS

Data from eight clinical pharmacokinetic studies in healthy volunteers employing single-dose study designs were evaluated covering oral doses of 50 to 200 mg. Only data from healthy volunteers were selected in order to minimize any influence of age or disease state. The volunteers were all within 10% of their ideal body weight and their ages ranged from 21 to 35 years. Exclusion criteria were similar for all studies. Simultaneous fenoldopam plasma and total urinary excretion data were available in 65 individuals. A total of 136 profiles was available due to the crossover design of some of these studies. The studies selected included single-oral dose ranging experiments, bioavailability and bioequivalence studies of a capsule or tablet formulation, drug interaction studies with acetaminophen, and various food effect studies. In none of these studies was there any evidence to suggest that changes in fenoldopam's systemic clearance were occurring. All the observed alterations were felt to be due to changes in fenoldopam presystemic metabolism with resulting changes in its bioavailability. All studies were conducted by SK&F-sponsored clinical pharmacology units worldwide using similar protocol designs and identical specimen handling techniques.

In addition to the information compiled on fenoldopam, limited data were obtained for fenoldopam-8-sulfate. Of the 136 profiles, data on fenoldopam-8-sulfate were available in 104.

All analytical determinations for fenoldopam or fenoldopam-8-sulfate were performed using the same analytical methodology (10). Three laboratories worldwide contributed data, and extensive assay validations and cross validations were conducted. Furthermore, no *in vitro* breakdown of the fenoldopam metabolites back to fenoldopam was observed in urine when analyzing authentic and spiked urine samples under various storage conditions. For example, urine samples spiked with the sulfate metabolites of fenoldopam (30 μg/ml—equal to that found after an oral dose of 200 mg fenoldopam) and then subjected to repeat analysis as a function of storage conditions and analytical procedures were found to convert less than 0.05% of the sulfates to fenoldopam. In addition, authentic urine samples subjected to repeat fenoldopam analysis as a function of storage time showed no change in the fenoldopam concentration.

The aggregate data represent all the available single-oral dose data for fenoldopam where simultaneous plasma and total urinary analyses were performed. Renal clearance for fenoldopam or fenoldopam-8-sulfate was calculated according to the following equation:

$$\mathrm{RCL} = X_u/\mathrm{AUC}$$

where X_u is the amount of fenoldopam or fenoldopam-8-sulfate excreted in the 0- to 24-hr urine postdosing and the corresponding AUC obtained via the trapezoidal rule. In some cases AUC measurements were available only up to 12 hr postdosing. Analysis of AUC_{0-24} data reveal that AUC_{0-12} estimates should be >95% of the actual AUC_{0-24} value.

In a pilot experiment to determine if desulfation of fenoldopam-8-sulfate occurs *in vivo,* one adult male beagle was studied on two separate occasions, receiving intravenous injections either of fenoldopam (1 mg/kg) or of fenoldopam-8-sulfate (4.4 mg/kg). The animal was maintained on its standard diet and housed in a metabolism cage equipped with automatic watering. After an overnight fast, the dose was administered and blood sampled at various intervals in heparinized vacutainers and centrifuged immediately at 4°C. Five milliliters of plasma was transferred to polyproplyene tubes containing 0.25 ml of 10% ascorbic acid as a preservative. Plasma determinations were conducted for fenoldopam and fenoldopam-8-sulfate using an HPLC-EC procedure previously reported (10). The quantifiable limits for fenoldopam and fenoldopam-8-sulfate were 0.1 and 5.0 ng/ml, respectively. Additionally, *in vitro* hydrolysis in spiked dog plasma of fenoldopam-8-sulfate to fenoldopam due to analytical procedures represented only 0.003% of the sulfate present. This result indicated that the plasma fenoldopam concentrations seen in the dog after iv administration of fenoldopam-8-sulfate were due mainly to *in vivo* back-conversion of the fenoldopam-8-sulfate.

RESULTS

In order to examine the nonlinear behavior of fenoldopam renal clearance, individual subject clearance values were plotted against their corresponding AUC values (Fig. 1). A similar plot was constructed for fenoldopam-8-sulfate (Fig. 2). Unlike fenoldopam-8-sulfate, which exhibited renal clearance values independent of AUC with an overall mean (±SE) of 129 ± 4 ml/min, fenoldopam exhibited a nonlinear decrease in renal clearance at increasing fenoldopam AUC. For reference, a single 100-mg tablet of fenoldopam under fasting conditions yields a fenoldopam AUC of approximately 30 ng × hr/ml. At the lower AUC, achieved through food-induced decreases in fenoldopam bioavailability and/or the use of smaller total oral doses, fenoldopam renal clearance exceeded 1000 ml/min. At the higher AUC values, renal clearance begins to asymptote at approximately 150 ml/min. In order to characterize the observed changes in fenoldopam

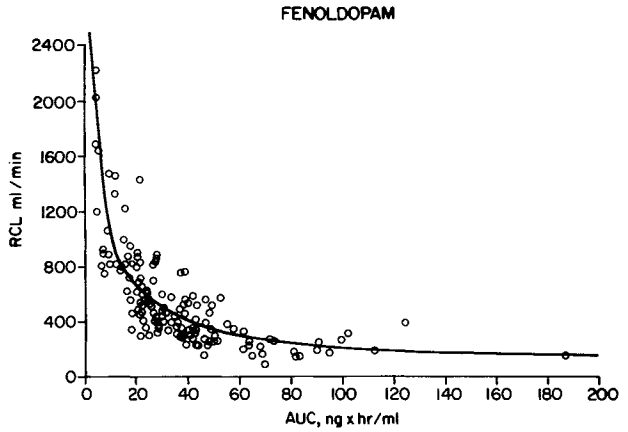

Fig. 1. Fenoldopam renal clearance versus AUC relationship in healthy volunteers. $Y = [2852 - (2852*X)/(5.2 + X)] + 78$; $N = 136$.

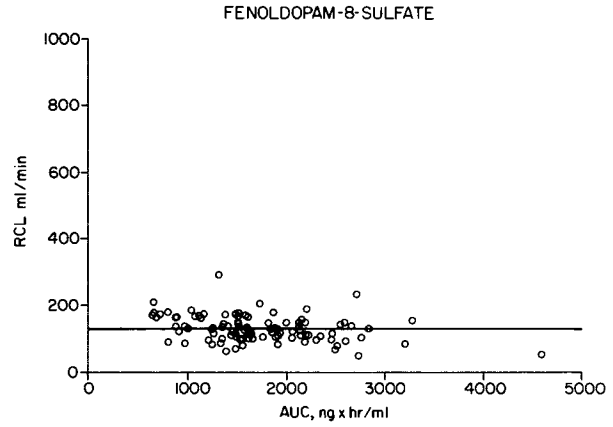

Fig. 2. Fenoldopam-8-sulfate renal clearance versus AUC relationship in healthy volunteers. Mean (±SE), 129 ± 4 ml/min; N = 104.

renal clearance, as a function of fenoldopam AUC, the following saturation model was employed:

$$RCl = (RCl_{Tmax} - (RCl_{Tmax} \times AUC)/(K'm + AUC)) + RCl_{GFR}$$

where RCl is the observed time-averaged renal clearance of fenoldopam, RCl_{Tmax} represents the maximum secretory renal clearance, $K'm$ is the AUC required to produce 50% of the RCl_{Tmax} value and RCl_{GFR} is the renal clearance of fenoldopam at maximum saturation. This equation is analogous to a classical saturation model (11). The RCl_{Tmax} was calculated as being 2852 ± 465 ml/min, with a RCl_{GFR} of 78 ± 58.6 ml/min and a $K'm$ of 5.2 ± 1.8 mg × hr/ml. At the reference AUC of 30 ng × hr/ml, the model predicts a significant decrease in fenoldopam renal clearance, representing only 15% of the maximum value. At the highest experimentally encountered AUC of 190 ng × hr/ml, approximately 98% inhibition was predicted.

DISCUSSION

The underlying mechanisms involved in the renal excretion of fenoldopam are unknown. Saturable renal tubular secretion, either cationic or catechol-specific transport (7), is probably involved. For this mechanism to be the only process involved requires that fenoldopam have a high affinity for the transport system considering the relatively low plasma concentrations of fenoldopam and the magnitude of the observed renal changes relative to the small changes in AUC. However, the involvement of tubular secretion alone cannot account for the elevated renal plasma clearances seen at low fenoldopam AUC. Although fenoldopam can increase renal blood flow (1,4), the magnitudes of these renal clearance values, when corrected for blood/plasma partitioning (1.2–1.5), are in excess of any observed renal blood flow in man. These calculated clearance values require that greater than 50% of cardiac output goes directly to the kidneys, with the blood flow changes being inversely related to the fenoldopam plasma concentrations. An alternate explanation is therefore necessary in order to account for these elevated values.

The metabolic capabilities of the kidney are only beginning to be fully appreciated. Glucuronidation, sulfation, methylation, and various other metabolic functions have been identified in the kidney (12–14). Intrarenal generation of fenoldopam from the metabolic breakdown of one or several of its circulating metabolites, coupled with its subsequent excretion into the urine, may be responsible for the unusual elevations noted in fenoldopam renal clearance. Some experimental data support this hypothesis.

Fenoldopam's two primary sulfated metabolites, fenoldopam-8-sulfate and fenoldopam-7-sulfate, have been shown, in our laboratory (17), to undergo desulfation *in vivo* in the dog, yielding fenoldopam. Figure 3 shows data obtained in one dog after iv fenoldopam or fenoldopam-8-sulfate administration. After administration of fenoldopam-8-sulfate, low circulating plasma levels of fenoldopam were achieved which declined in parallel with fenoldopam-8-sulfate, indicative of reversible metabolism. Both sulfated metabolites have been pharmacologically tested and have the ability to increase renal blood flow in the dog *in vivo;* however, neither possesses any direct activity in various *in vitro* models of DA_1 agonist activity. Since the relative AUC for the sulfated metabolites are 60–120 times greater than for fenoldopam itself and the percentage of the dose actually excreted in the urine as unchanged fenoldopam is less than 1%, only a small percentage of the sulfates and/or other metabolites needs to be converted back to fenoldopam during their passage through the kidney in order metabolically to inflate the renal clearance calculation for fenoldopam. Saturation of this minor metabolic pathway may occur, resulting in a decrease in its overall contribution at elevated fenoldopam AUC, thereby accounting for the observed changes in fenoldopam renal clearance.

The site of fenoldopam desulfation in the dog is unknown. Presumably several organs are involved, including the kidney, which has been shown to possess sulfatase activity (15). The renal desulfation of a sulfated metabolite back to the parent compound has been demonstrated for estrone sulfate (16). A similar mechanism may exist for fenoldopam. Also, considering the 12% free fraction of fenoldopam in human plasma and the observed renal clearance of 150 ml/min at the highest experimentally achieved fenoldopam AUC, some form of active renal secretion must be involved. Saturation of this component at elevated fenoldopam AUC may also be contributing to the observed nonlinear decreases in fenoldopam renal clearance.

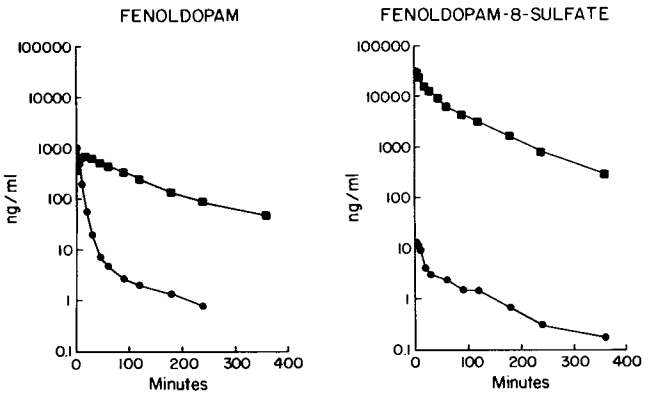

Fig. 3. Plasma concentrations of fenoldopam (●) and fenoldopam-8-sulfate (■) in one dog after intravenous fenoldopam (1.0 mg/kg) or fenoldopam-8-sulfate (4.4 mg/kg) administration.

This analysis confirmed a nonlinear relationship between fenoldopam renal clearance and AUC, indicative of saturable renal excretion occurring in man. The retrospective approach utilized in this report provided information on the intrasubject differences and proved to be a useful technique for detecting nonlinear excretion in a large population of subjects. Saturable renal excretion of fenoldopam within a given dosing interval likely occurs but the experimental data demonstrating this hypothesis are unavailable. The mechanisms involved in fenoldopam's nonlinear excretion, consistent with the available experimental data, include the apparent saturable intrarenal production of fenoldopam from one or more of its metabolites coupled with active tubular secretion of fenoldopam. The ability of the kidney to metabolize basic compounds during their transport across the kidney has been documented for morphine as well as for catechol itself (7). The result with fenoldopam raises the possibility of reversible intrarenal metabolism and its possible influence on renal clearance determinations.

Fenoldopam renal excretion is a complex phenomenon which will require extensive study before it is fully understood. Coupled with its ability to increase renal blood flow, fenoldopam should prove to be an intriguing drug for studying renal excretion and metabolism.

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