Pharmacokinetic and Dynamic of Furosemide in Peritoneal Dialysis Patients

The aim of our study was to evaluate the efficacy and bioavailability of a commonly used oral furosemide dose (500 mg) compared to a 250 mg intravenous (IV) dose in PD patients with significant residual renal function (urine volume > 100 mL). We also evaluated the immediate blood pressure effect in these patients. The data were obtained from a study we performed for the homologation of a 500-mg dose of furosemide by Health Canada.

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Patients on peritoneal dialysis (PD) with significant residual renal function have better fluid balance and less exposure to hyperosmolar glucose dialysate. Moreover, the re-analysis of the Canada-USA (CANUSA) study demonstrated that for each additional 250 mL of urine excreted per day, the relative risk of death was decreased by 36% (1). To maximize fluid balance, loop diuretics are commonly used. However, there are no clear recommendations about their use. Indeed, in a study published by Flinn *et al.* on the effectiveness of furosemide in patients on PD, there was a large variability in the mean daily doses of furosemide, ranging from 40 mg to 250 mg (2). Furthermore, very few pharmacokinetic and dynamic data on furosemide in PD patients are available, and most of them have been published using high doses of furosemide (e.g. 1 g twice a day), which are less used nowadays (3). Consequently, few studies have used lower daily doses of furosemide (e.g. 500 mg), currently used in clinical practice (4).

Although furosemide is mainly used for sodium retention, there is still controversy around its hypotensive effect (5,6). The blood pressure (BP)-lowering effect of furosemide is mainly explained by a reduction in plasma volume. However, some studies point out a possible

immediate vascular effect (5). Several mechanisms seem to be involved, including inhibition of the cotransporter NKCC1 on vascular smooth muscle cells and vascular prostaglandin synthesis.

We evaluated the efficacy and bioavailability of a commonly used oral furosemide dose (500 mg) compared to a 250 mg intravenous (IV) dose in PD patients with significant residual renal function. We also evaluated the immediate BP effect in these patients.

MATERIALS AND METHODS

The study was carried out in 12 patients on PD for an average of 22 ± 13.15 months. All patients were on chronic oral furosemide. After a washout period of 7 days, 12-hour urine was collected for volume, as well as sodium and potassium measurements, before and after a 500 mg oral dose of furosemide. Blood pressure was also measured before the administration of the medication, at 30 minutes, and at 1, 2, 4, 6, and 12 hours. The same protocol was repeated with a 250 mg of IV furosemide after another washout period of 7 days. Furosemide blood levels were measured up to 96 hours after the oral and IV doses for pharmacokinetics calculations. Ethical approval was obtained by the institutional review board of our institution. Informed consent was also obtained for each patient.

RESULTS

One patient was excluded for no significant residual renal function at the time of the study. Four women and 7 men with a mean age of 51.7 ± 14.4 years old were studied. Mean oral dose of furosemide before the study was 325.45 ± 183.32 mg. There was a statistically significant increase of urine volume and fractional excretion of sodium (FeNa) and potassium (FeK) after the oral dose (Table 1). Urine volume and sodium excretion ($U_{Na}V$) increased by 379.3 ± 537.3 mL and 53.7 ± 82.9 mmol, respectively. A patient was excluded from the IV study for incomplete urine collection. A 250-mg dose of IV furosemide was associated with significant increase of urine volume and sodium and potassium excretion (Table 1). Urine volume and $U_{Na}V$ increased by 386.4 ± 624.0 mL and 57.1 ± 94.6 mmol, respectively. Efficacy was not statistically different between oral and IV dose. Plasma pharmacokinetic data showed 50% bioavailability of the oral dose. There was a significant but small increase of potassium excretion after both the oral and IV dose (Table 1).

In a mixed model analysis, there were no significant differences between systolic and diastolic with both oral and IV furosemide up to 6 hours post-dose (Figure 1). Specifically, BP was the same at baseline and 30 minutes after furosemide administration ($139 \pm 15 / 76 \pm 11$ to $137 \pm 20 / 78 \pm 15$ mmHg, $p > 0.50$, for oral, and $137 \pm 22 / 78 \pm 11$ to $136 \pm 21 / 79 \pm 11$ mmHg, $p > 0.55$ for IV). The drop in systolic BP at 12h became significant (-6.92 mmHg, $p = 0.009$) with the oral dose only.

TABLE 1
Efficacy of 500 mg of Oral and 250 mg of IV Furosemide

	Furosemide	Period 1 (-12 - 0)	Period 2 (0 - 12)	P value
FeNa (%)	oral	4.6±3.9	13.6±9.5	<0.001
	IV	4.7±3.8	13.7±10.8	0.006
FeK (%)	oral	42.1±21.1	66.6±31.0	<0.001
	IV	47.8±25.0	76.7±47.4	0.02
Volume (mL)	oral	413.0±401.7	792.3±899.9	0.02
	IV	425.3±466.6	811.6±1064.9	0.04
U _{Na} V (mmol/12 hours)	oral	27.6±32.6	81.2±113.7	0.03
	IV	28.4±38.4	85.5±129.6	0.04
U _K V (mmol/12 hours)	oral	9.5±12.2	13.5±13.5	0.05
	IV	9.0±8.9	13.6±16.2	0.05

IV = intravenous; FeNa = fractional excretion of sodium; FeK = fractional excretion of potassium; U_{Na}V = urine sodium excretion; U_KV = urine potassium excretion.

Figure 1 — Effect of 500 mg of oral and 250 mg of IV furosemide on mean blood pressure (mmHg). IV = intravenous.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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DISCUSSION

The appropriate dosage of furosemide in PD patients remains a clinical challenge, especially because there are few pharmacokinetic data. Our study demonstrates that a 500 mg oral dose of furosemide in PD patients with significant residual renal function is effective in improving urine output and sodium excretion. The magnitude of the effect is of clinical significance and can be expected to be associated with easier control of volume and possibly has a significant impact on PD technical and patient survival. Also, the furosemide doses do not induce immediate BP reduction in PD patients. *In vivo* arterial response may occur only at supratherapeutic concentration, which is not achieved in a real clinical context (5).

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