THE RELATIONSHIP BETWEEN PHARMACOKINETIC VARIABLES AND PHARMACODYNAMIC PROFILES OF BOLUS VERSUS CONTINUOUS INFUSION OF FUROSEMIDE IN CRITICALLY ILL PATIENTS

[1]MOJTABA MOJTAHEDZADEH, [1]MARIA TAVAKOLI ARDAKANI, [1]EBRAHIM SALEHIFAR, [2]ATABAK NAJAFI, [2]MOHAMMAD REZA KHAJAVI, [3]MAJID MOEINI, [4]SIMA SADRAY

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, [2]Department of Anesthesiology, Faculty of Medicine, [3]Department of Surgery, Faculty of Medicine, [4]Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

In this investigation, the pharmacokinetic variables of continuous infusion and intermittent bolus injection of furosemide and the possible relationship between its pharmacokinetic characteristics and pharmacodynamic profile among intensive care unit (ICU) patients were studied.

In this prospective, randomized, clinical trial, twelve patients received IV bolus of 20 mg of the drug during 3 hours period and, the drug dose was doubled, when the urine output was less than 1 ml/kg/h (group 1). The other nine patients received a continuous intravenous furosemide infusion at the rate of 0.1 mg/kg/h (group 2). The amount of furosemide in serum was measured by high performance liquid chromatography (HPLC).

Results showed a positive correlation between plasma clearance of furosemide and its diuretic activity (P=0.01). The pharmacokinetic parameters such as V_d (l), CL (ml/min), K_e (min^{-1}) and $t_{½}$ (min) in continuous infusion patients were not significantly differed from the bolus patients (P-values 0.5, 0.9, 0.9, 0.9, respectively). Nevertheless the observed plasma clearance of drug in the continuous infusion group was clinically higher than bolus injection group and as a result the cumulative urine output per hour per mg of furosemide in a continuous infusion was observed to be higher than bolus(P=0.2). Changes in serum sodium and potassium were similar for both groups, but bolus injection patients were associated with higher potassium depletion (P=0.001). Therefore, continuous infusion seems to be better means of diuretic therapy in critically ill patients.

Keywords: Furosemide, Pharmacokinetics, Pharmacodynamic, Bolus, Infusion

INTRODUCTION

One of the common problems in ICU patients is positive fluid balance that may results from the received of large amount of IV fluids, TPN (total parenteral nutrition), and in gastric gavage diseases such as renal failure and CHF (Congestive Heart Failure). This problem along with hemodynamic instability in critically ill patients and those electrolyte imbalances, especially with cardiac, pulmonary, and renal insufficiency, may cause pulmonary and peripheral edema and electrolyte imbalances. These complications may require positive mechanical ventilation and increased in days of staying in ICU (1- 3).

Furosemide is a potent diuretic agent with rapid action, which is used in clinical practice to treat edematous state in congestive heart failure, nephrotic syndrome, and liver cirrhosis, and exerts its effects through the luminal side of the thick ascending limb of the loop of henle, where it inhibits reabsorption of chloride and sodium (4-7). It has been shown that the diuretic effect of furosemide in patients with refractory congestive heart failure could be controlled more effectively if it is administered by continuous infusion (8). In an animal study it was found that natriuretic and diuretic efficiencies of furosemide were greater with continuous infusion compared with bolus administration (9). Several studies have similarly reported that furosemide natriuretic and diuretic effects were greater than expected when the input rate of drug was slowed by an IV infusion (5, 10, 11).

Correspondence: Sima Sadray, Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran, E-mail: sadrai@sina.tums.ac.ir

Comparative data from previous investigations suggest that both the activity and disposition of furosemide may differ as a function of age, diseases (such as renal disease, CHF, liver disease and hypertension), hydration state and plasma protein content. However, critically ill patients often present some pathophysiological conditions that may frequently alter the pharmacokinetic behavior of furosemide (12-15).

Since none of these studies have been conducted in the critical care settings, the following study was conducted to determine the relationship between pharmacokinetic variables and physiological effects of furosemide in both groups of continuous infusion and intermittent bolus, in ICU patients.

PATIENTS AND METHODS

Study design

The study population consisted of 21 critically ill patients who were admitted to ICU of Sina hospital and required diuretic drug therapy. The ethic committee at TUMS (Tehran University of Medical Science) approved the study.

Exclusion criteria were: 1) pregnancy; 2) history of sensitivity or intolerance to furosemide; 3) clinical evidences of dehydration such as systolic blood pressure/heart rate (SBP/ HR)<1 or mean arterial pressure (MAP) <60 mmHg or CVP<8mmHg; 4) electrolyte imbalances (potassium <3mmol/l, sodium < 130 mmol / l); 5) patients had received another diuretic within the last 12 hours; 6) hypotension with a systolic blood pressure (SBP)<90mmHg; 7) hypo-albuminaemia (Albumin<3.5g/dl); 8) patients receiving renal replacement therapy such as hemodialysis, peritoneal dialysis; 9) patients with renal dysfunction (creatinine clearance <50 ml/min); (10) hepatic impairment (liver enzyme>3 times of normal value; 11) patients with blood urea nitrogen (BUN) more than 40 mg/dl and 12) patients with bicarbonate level of more than 28 mEq/l.

The study was a randomized open label clinical trial comparing intermittent intravenous bolus administration of furosemide versus continuous infusion. The fluid intake was by oral (500 – 700 $mL/24_{hours}$) and by intravenous (2000 $mL/24_{hours}$). Treatment in either group was based on a specified algorithm according to the patient's net hourly fluid balance. Both regimens were titrated individually to an hourly net fluid balance of at least 1 ml/kg. Once this objective was achieved, the dosing of furosemide was adjusted if necessary to ensure that hourly urine output was at least 1 ml/kg until the end of therapy (determined by the attending physicians). In situation where any complications occurred which require diuretic discontinuation, the patient was removed from the study and managed accordingly. Patients were divided to two groups.

Group 1 (Intermittent furosemide bolus administration): After an initial IV 20 mg, drug dose was doubled during 3 hours (maximum in each dose: 320 mg) when urine output was less than 1 ml/kg/h.

Group 2 (continuous furosemide infusion): 250 mg of furosemide was diluted with 250 ml of 5 percent dextrose solution. Patients in the infusion group received intravenous furosemide continuously at 0.1 mg/kg/h.

Methods

Serum Measurements:

Blood samples were collected at the time of 0, 10, 30, 60, 90 and 360 minutes to determine pharmacokinetic parameters following diuretic therapy. Hemodynamic state of each patient (heart rate, mean arterial pressure, central venous pressure) and urine output were recorded before and after furosemide administration.

Acute Physiology and Chronic Health Evaluation Scoring System (APACHE II), sodium, potassium, BUN, creatinine, calcium, phosphate and arterial blood gas were monitored at the beginning of the study and also at times of 6, 12 and 24 hours following diuretic therapy. During the study period (12 hours) baseline data were collected for each patient including: a) demographic data and severity of illness using the APACHE II scoring system (16). (b) diagnosis and reason for admission to the ICU; c) hemodynamic variables (mean arterial pressure, heart rate, central venous pressure) and d) the list of all the medications being administered.

HPLC system:

In this study, a rapid, sensitive and selective reversed phase HPLC assay using U.V detector was employ (17). Acetonitril-water (30:70) containing 5mM K_2HPO_4/KH_2PO_4 was used as the mobile phase. The pH of buffer solution was adjusted to 4.25 with phosphoric acid. Flow rate and injection volumes were 0.9 ml/min and 40µl respectively. The detection wavelength and detection limit of drug were 235 nm, 20 ng respectively. The intra-assay coefficient of variation of the method for furosemide in plasma was always less than 10% (17, 18).

Pharmacokinetic analysis:

Pharmacokinetic parameters for furosemide were determined by standard methods. The terminal elimination rate constant (k_e) was calculated from the negative slope of the terminal log – linear portion of the plasma concentration – time curve by linear regression of the natural logarithm of

plasma concentration against time. Half-life ($t_{½}$) was calculated from the equation of $0.693/k_e$. The maximum plasma concentration (C_{max}) was taken directly from the data. Volume of distribution (V_d) was calculated by dividing the dose by C_{max} (maximum concentration), and total clearance was calculated by multiplying k_e and V_d (19).

Statistical analysis:

Data are presented as mean+/_SD. Statistical analysis was performed on a personal computer with the SPSS 11.0.Statistical analysis included Fishers Exact Test for percent comparisons and Mann Whitney Test for quantitative variables.

RESULTS

Twenty-six patients were enrolled into the study. Five patients had to be excluded because of hemodynamic instability and electrolyte im-balances. Twelve patients were randomly assigned to the intermittent bolus group and nine patients were given a continuous infusion of furosemide.

Baseline characteristics for both groups at the time of entry to the study are compared in Table 1.

Urine output at different time intervals in both groups are shown in table 2. There was no significant difference in urine output at different time intervals between two groups.

Cumulative hourly urine output per mg of furosemide in the continuous infusion group was higher than intermittent bolus group, but it was not significant (table 3, P=0.2).

Cumulative hourly urine output in the intermittent bolus group was higher in comparison with continuous infusion group; nevertheless, in this case also it was not significant (table 3, P=0.4).

Pharmacokinetic parameters for the two groups are compared in table 4.These calculated parameters were very similar for both treatment groups. The changes in serum sodium and potassium level were also similar (table 5).

Changes in serum sodium and potassium with time in continuous infusion group and intermittent bolus group are shown in table 6.

It was found that decrease of potassium in bolus group was higher than continuous infusion group (table 6, P=0.001). Correlation between pharmacokinetic parameters and cumulative urine output after 12 hours is shown in table 7.

DISCUSSION

The aim of this study was to evaluate the relationships between pharmacokinetic variables and physiological effects of furosemide by two methods of continuous infusion and intermittent bolus administration, in critically ill patients.

Various studies have shown the potential benefits of the use of continuous furosemide infusions in patients with congestive heart failure refractory to normal doses of furosemide (8, 20, 21).

Table 1. Basline clinical features at the time of entry into the study (mean ± SD)

	Continuous Infusion	Intermittent Bolus
Age (year)	57.4±20.3	55.7±16.8
Sex (F/M)	(6/3)	(4/8)
APACHE II	13±5	15±5
Primary Diagnosis		
CHF	1	1
Multiple Trauma	2	2
ICH	1	1
Sepsis	0	1
Anaphylactic shock	0	1
Pneumonia	0	1
ladder tumor	0	1
Liver cirrhosis	0	1
GI bleeding	1	0
COPD	2	2
Cerebral edema	2	1
Mechanical Ventilation	7	7
Dopamine	3	2
Dobutamine	5	3
Nitroglycerin	0	1
ACE inhibitors	2	2

APACHE II Score, Acute Physiology and Chronic Health Evaluation II Scoring System; ACE inhibitors, angiotensin converting enzyme inhibitors; CHF, congestive heart failure; GI bleeding, gastrointestinal bleeding; ICH, intra cranial hemorrhage; COPD, chronic obstructive pulmonary disease.
No significant differences between groups were noted.

It has been found that there were no significant differences in total urine volume after 12 hours between bolus injection and continuous infusion of furosemide after cardiac surgery. Consistent with results of this study it has been reported that variation of diuresis during continuous infusion from hour to hour after bolus injection was low and was sustained throughout the infusion period (22).

While it has been shown that changes in serum sodium and potassium levels are similar in both groups (22, 23), the results of this study showed that potassium decreased significantly (P=0.001) in bolus group (table 6) but during continuous infusion phase, changes in serum sodium and potassium at 6, 12 and 24 hours after furosemide infusion were not significant (table 5).

The results of this study which was conducted on patient was different from results of a randomized, crossover double blind study in healthy volunteers in which the time course of furosemide delivery in the proximal renal tubule was an important determinant of diuretic response (10).

Table 2. Mean urine output at different time intervals in two groups

Time (min)	Continuous infusion Urine output (ml)	Intermittent bolus Urine output (ml)	P-value
0-10	30.0 ± 17.5	42.1 ± 60.1	0.6
10-30	66. 2 ± 51.1	160.7 ± 186.9	0.4
30-60	90.3 ± 83.9	125.9 ± 115.4	0.7
60-90	52.0 ± 28.0	86.2 ± 118.1	0.6
90-120	67.4 ± 39.3	77.8 ± 85.1	0.7
120-360	320.5 ± 294.8	293.7 ± 88.3	0.5
360-720	473.9 ± 482.4	552.9 ± 244.3	0.13

There is not significant difference between groups.

Table 3.Mean hourly urine output of furosemide in two groups

	Continuous infusion	Intermittent bolus	P-value
Mean hourly urine output (ml/hour)	92.2± 56.3	116.2±35.2	0.4
Mean hourly urine output per mg of furosemide (ml/hr/mg)	9.3±7.5	4.8±3.4	0.2

There is no significant difference between groups.

Table 4. Mean ± SD pharmacokinetic parameters of furosemide after continuous infusion and intermittent bolus administration to critically ill patients.

Kinetic parameters	Continuous infusion	Intermittent bolus	P-value
CL (mL/min)	161±134	138±74	0.9
V_d (L)	12.2±5.1	12.2±7.2	0.5
k_e (1/min)	0.0112±0.0064	0.0121±0.0069	0.9
$t_{1/2}$(min)	111.0±121.3	73.3±42.8	0.9

CL, clearance; V_d Volume of distribution; k_e, elimination constant; $t_{1/2}$, half – life
There is no significant difference between groups.

Table 5. Serum sodium and potassium changes

	Sodium (mEq/l)			Potassium (mEq/l)		
Time (hr)	Continuous infusion	Intermittent bolus	P-value	Continuous infusion	Intermittent bolus	P-value
0	139.22±5.80	140.42±5.40	0.7	4.33±1.18	4.56±0.80	0.3
6	137.11±5.88	138.08±5.76	0.7	4.11±0.84	4.08±0.75	0.9
12	137.67±6.89	138.25±5.97	0.6	4.23±0.56	4.12±0.54	0.6
24	139.11±7.66	138.08±7.18	0.8	3.94±0.61	3.75±0.72	0.5

There is no significant difference between groups.

Table 6. Serum potassium and serum sodium changes in continuous infusion group

Group	Time (h)	0	6	12	24	P-value
Continuous infusion	Serum K(mEq/l)	4.56±0.80	4.08±0.75	4.12±0.54	3.75±0.72	0.001*
	Serum Na(mEq/l)	140.42±5.40	138.08±5.76	138.25±5.97	138.08±7.18	0.2
Bolus	Serum K(mEq/l)	4.33±1.18	4.11±0.84	4.23±0.56	3.94±0.61	0.6
	Serum Na(mEq/l)	139.22±5.80	137.11±5.88	137.67±6.89	139.11±7.66	0.5

No significant difference., *P<0.05 is significant

Table 7. Correlation between pharmacokinetic parameters and cumulative urine output after 12 hours.

Parameters	Spearman's coefficient	P-value
CL(mL/min)	0.54	0.01*
$k_e(min^{-1})$	0.26	0.2
$t_{1/2}$(min)	-0.46	0.03*
V_d(L)	0.59	0.005*

* P<0.05 is significant

In another study a variations in urine output in the intermittent furosemide group were greater than the continuous infusion group and it has been concluded that patients who were hemodynamically unstable should be given a continuous infusion because urine output in this case will be more predictable (24).

While a protocol for administration of furosemide by bolus and continuous has been reported but the relationship between pharmacokinetic parameters and pharmacodynamic effect of two protocols have not been evaluated. In this study a similar protocol guided diuretic therapy with an interest to investigate the disposition of the drug in an ICU setup was conducted. In contrast to results of a study that both protocols of standardized fluid management therapy were equally effective in achieving net diuresis, the continuous infusion furosemide group had a more negative fluid balance, although not statistically different from the standardized bolus furosemide group. The results of this study was similar to results of a report (1) in which, pharmaco-dynamic effects of furosemide in both groups were not significantly different.

Since none of these studies had evaluated the pharmacokinetic profile of continuous infusion versus intermittent bolus of furosemide in heterogeneous group of critically ill patients, this study was designed to assign these parameters and the relationship between pharmacokinetic and pharmacodynamic response of furosemide in critically ill patients. The results of the present study illustrates, that there is a positive relationships between plasma clearance, volume of distribution and diuretic effects of furosemide in critically ill patients (P- values 0.01 and 0.005 respectively).

It was found that when plasma clearance and volume of distribution of furosemide increases, the cumulative urine output after 12 hours also increase.

Furosemide is eliminated via kidneys and the rate of renal excretion is directly proportional to the plasma concentration, which is important when the relationship between the diuretic effect and drug's level at the site of action (23).Therefore increase in plasma clearance shall be associated with increase in diuretic effect. Our results show that mean urine output per hour per mg of furosemide in continuous infusion treatment group, was higher than intermittent bolus although it was not significant. Higher plasma clearance for continuous infusion may be the possible explanation for this effect. Our findings in contrast to a report (25) have confirmed that drug presence in the site of action must be more relevant for its diuretic effect than its plasma concentration.

CONCLUSIONS

This concluded that the input rate of furosemide administration has no effect on derived pharmacokinetic variables. However, there are some correlation between these parameters (plasma clearance, half-life, volume of distribution) and pharmacodynamic response (urine output) of furosemide. In addition, it was found that plasma clearance of furosemide during continuous infusion were higher than intermittent bolus, although not statistically significant. Intermittent administration was associated with greater fluctuation in urinary output and greater serum potassium decrease. Urinary output per hour per dose of furosemide was higher and was more consistent in continuous infusion.

REFERENCES

1. Schuller D, Lynch JP, Fine D. Protocol guided diuretic management: Comparison of furosemide by continuous infusion and intermittent bolus. Crit Care Med 1997; 25:1969-1975.
2. Schuller D, Mitchell JP, Calandrino FS, Schuster DP. Fluid balance during pulmonary edema. Is fluid gain a marker or a cause of poor outcome. Chest 1991; 100: 1068 – 1075.
3. Humprey H, Hall J, Sznajder I. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. Chest 1990; 97:1176-1180.
4. Kaojaren S, Day B, Brater DC. The time course of delivery of furosemide into the urine: an independent determinant of overall response. Kidney Int 1982; 22: 69-74. !
5. Lee MG, Li T, Chiou WL. Effect of intravenous infusion time on the pharmacokinetics and pharmacodynamics of the same total dose of furosemide. Biopharm Drug Dispos 1986; 7: 537-47.

6. Alvan G, Helleday L, Lindholm A, Sanz E, Villen T. Diuretic effect and diuretic efficiency after intravenous dosage of furosemide. Br J Clin Pharm 1990; 29: 215-90.
7. Brater DC. Pharmacodynamic considerations in the use of diuretics. Ann Rev Pharmacol Toxicol 1983; 23: 24-62.
8. Lawson DH, Gray JMB, Henry DA, Tilstone WJ. Continuous infusion of furosemide in refractory edema. BMJ 1978; 2: 476.
9. Castaneda – Hernandez G, Verges J, Pichette V, Heroux L, Caille G, Du-souich P. Input rate as a major determinant of furosemide pharmacodynamics: influence of fluid replacement and hypoalbuminemia. Drug Metab Dispos 2000; 28: 323-328.
10. Van Meyel JJM, Smiths P, Russel FGM, Gerlag PGG, Tan Y, Gribnav FWT. Diuretic efficiency of furosemide during continuous administration versus bolus injection in healthy volunteers. Clin Pharmacol Ther 1992; 51: 440-444.
11. Wakelkamp M, Alvan G, Paintaud G. Natriuretic efficieny of furosemide as a consequence of drug input rate. Br J Clin Pharmacol 1997; 43: 481-491.
12. Tilstone WJ, Fine A. Furosemide kinetics in renal failure. Clin Pharmacol Ther 1978; 23:644-650.
13. Beerman B, Dalen E, Lindstrom B. Elimination of furosemide in healthy subjects and in those with renal failure. Clin Pharmacol Ther 1977; 22:70-78.
14. Brater DC, Seiwell R, Anderson S, Burdette A, Dehmer GJ, Chennavasin P. Absorption and disposition of furosemide in congestive heart failure. kidney Int 1982; 22:171-176.
15. Kerremans AL, Tan Y, Van Baar H, Van Ginneken CAM, Gribnau FWJ. Furosemide kinetics and dynamics in aged patients. Clin Pharmacol Ther 1983; 34:181-189.
16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13: 818-829.
17. Barroso MB, Jimenez RM, Alonso RM, Ortiz E. Determination of piretanide and furosemide in pharmaceuticals and human urine by high – performance liquid chromatography with amperometric detection. J Chrom B 1996; 675: 303-312.
18. Abou – Auda HS, Al – Yamani MJ, Morad AM, Bawazir SA, Khan SZ, Al – Khamis KI. High – performance liquid chromatographic determination of furosemide in plasma and urine and its use in bioavailability studies. J Chromatogr B 1998; 710: 121-128.
19. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther 1995; 57: 601-609.
20. Krasna MJ, Scott GE, Scholz PM. Postoperative enhancement of urinary output in patients with acute renal failure using continuous furosemide therapy. Chest 1986; 89:294-295.
21. Rudy DW, Voelker JR, Green PK, Loop diuretics for chronic renal insufficiency. A continuous infusion is more efficacious than bolus therapy. Ann Intern Med 1991; 115:360-366.
22. Copeland JG, Campbell DW, Plachetka JR, Salmon NW, Larson DF. Diuresis with continuous infusion of furosemide after cardiac surgery. Am J Surg 1983; 146: 796-90.
23. Magovern JA, Magovern GJ. Diuresis in hemodynamically compromised patients continuous furosemide infusion. Ann Thorac Surg 1990; 50: 482-484.
24. Klinge JM, Scharf J, Tlofbeck M, Gerling S, Bonakdar S, Singer H. Intermittent administration of furosemide versus continuous infusion in the postoperative management of children following open heart surgery. Intensive Care Med 1997; 23: 693-697.
25. Alvan G, Paintaud G, Wakelkamp M. The efficiency concept in pharmacodynamics. Clin Pharmacokinet 1999; 36: 75-389.