Safety of Continuous rFVIII-FS Infusions via 8-hour 250cc 0.9 IV bag

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Abstract

STATEMENT OF THE PROBLEM: The safety and efficacy of continuous rFVIII-FS infusions has been documented. A variety of methods of continuous infusions have been used by Hemophilia Treatment Centers (HTCs), most often with a mini-pump not widely available in some areas. rFVIII-FS is known to adhere to the polyethol-gylcol IV tubing, potentially affecting accurate dosing of factor.

AIM: This study identified the safety and efficacy of continuous infusion using a 250cc 0.9 NS IV bag via standard pump every 8 hours without additional infection risk.

METHOD: 10 hemophilia A subjects participated. Subjects received bolus rFVIII (Kogenate FS ™) infusion with pre and 1-hour post rFVIII-FS levels determining FVIII recovery. On the day of 8-hour continuous infusion, subjects received bolus rFVIII-FS for correction to 100% followed by individually calculated continuous infusion rFVIII in 250 cc 0.9 NS. rFVIII levels were drawn from the IV bag and peripherally at time points: pre-infusion, 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, and 8-hour. Blood cultures time points were drawn from the IV-bag and IV tubing pre-infusion, 4-hour, and 8-hour.

RESULTS: Fourteen subjects agreed to participate; 4 failed to follow up,10 subjects were included in analysis; 7 severe, 2 moderate, and 1 mild; Age range 26–62 years; Ethnicity of 5 African American, 4 Caucasian, and 1 Hispanic. The ranges of rFVIII-FS were 65–135% (blood) and 62-200% (bag). Serum rFVIII-FS levels remained stable throughout the 8-hour time period despite a decrease in rFVIII-FS levels in the IV bag consistent with previous rFVIII-FS continuous infusion studies, although this was not statistically significant (p-value range 0.36 to 0.9). A total of 60 time points of cultures during the study were negative. All subjects tolerated the 8-hour infusion without reported adverse events or inhibitor development.

CONCLUSIONS: The alternative delivery method and safety of 8-hour continuous infusions of rFVIII-FS has been confirmed and well tolerated by all subjects. This method can be helpful where mini-pumps are not available, allowing a standard safe delivery of rFVIII-FS continuous infusion by available means.

Statement of the Problem

- The safety and efficacy of continuous rFVIII-FS infusions has been documented. A variety of methods of continuous infusions have been used by Hemophilia Treatment Centers (HTCs), most often with a mini-pump not widely available in some areas.
- rFVIII-FS is known to adhere to the polyethol-gylcol IV tubing, potentially affecting accurate dosing of factor.

Aim

- **Identify the safety and efficacy of continuous infusion using a 250cc 0.9 NS IV bag via standard pump every 8 hours without additional infection risk.**

End Points

Primary End Point: Determine the bioavailability of FVIII given as a continuous infusion. Bioavailability is determined as a FVIII target range of 95-105% during an 8 hour period when measured hourly

Secondary End Point: Confirm safety of FVIII continuous infusion with no adverse events

Review of the Literature

•The use of plasma-derived and recombinant Factor VIII products for continuous infusion has been well described in the literature. [1-7, 9]

•The use of continuous factor VIII infusions for in patient management can use 30% less concentrate when compared to conventional (bolus) Factor VIII replacement. [4]

•Martinowitz et al. [6] were able to document a reduction of factor VIII concentrate use by 50% when using continuous infusion and still maintain hemostasis.

•Hurst et al [5] identified recombinant Factor VIII stability (Kogenate) when used as a mini-pump set-up over 168 hours.

•Bartorova [1] demonstrated improved efficacy and safety with use of continuous infusion systems with reduction in treatment cost when compared with bolus injections

•Bidlingmaier [2] compared continuous infusion of factor VIII with bolus injections achieving adequate factor VIII levels which were highly predictable as well as saving 30% of factor VIII infusion needs.

•Woloschuk & Schwetz [7] information paper outlines the guidelines for utilizing continuous infusion of factor VIII with mini-pump vs. IV 250cc infusion.

•DiMichelle [9] et al. tested the recovery of FVIII using four delivery systems during 8 hours of continuous infusion. When reconstituted in normal saline in a polyvinylchloride bag, recombinant factor recovery dropped to 57-76% at time 0 level, before re-approximating at 2 hours.

• Parti [8] et al. assessed the stability during simulated continuous infusion where an immediate 14-42% loss of FVIII activity was observed. It is suggested that binding to the delivery system occurs with eventual saturation.

• Dingli et al [3] documented 45 procedures utilizing continuous factor VIII infusions with 100% hemostasis achieved with maintained factor VIII levels within 46-191%, concluding the safety and efficacy of continuous infusion practices.

Method

- 10 hemophilia A subjects participated after approval of IRB.
- 1st visit; Subjects received bolus rFVIII (Kogenate FS ™) infusion with pre and 1-hour post rFVIII-FS levels determining FVIII recovery.
- 2nd Visit; 8-hour continuous infusion, subjects received bolus rFVIII-FS for correction to 100% as identified via recovery studies, followed by individually calculated continuous infusion rFVIII in 250 cc 0.9 NS.
- rFVIII levels were drawn from the IV bag and peripherally at time points: pre-infusion, 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, and 8-hour.
- Blood cultures were drawn from the IV-bag and IV tubing pre-infusion, 4-hour, and 8-hour time points.

Laboratory rFVIII values

PT ID		pre infusion	1 hr post	2 hr post	3 hr post	4 hr post	5 hr post	6 hr post	8 hr post	date of service
#01 +	Serum	7%	130%	165%	195%	196%	174%	158%	147%	3/29/2011
	IV bag	100%	103%	113%	111%	92%	107%	101%	97%	
# 02 **	Serum									DECEASED
	IV bag									
# 03 +	serum	11%	129%	124%	111%	109%	117%	112%	114%	3/2/2011
	IV bag	100%	107%	138%	48%	98%	155%	171%	26% ***	
# 04 +++	serum	0.36%	92%	88%	82%	74%	85%	70%	65%	3/16/2011
	IV bag	100%	91%	96%	92%	124%	119%	122%	137%	
#05 +++	serum	0.40%	114%	111%	116%	123%	128%	126%	141%	5/11/2011
	IV bag	100%	124%	117%	117%	107%	115%	97%	101%	
# 06 +++	serum	1.54%	110%	97%	110%	119%	105%	108%	100%	5/3/2011
	IV bag	100%	183%	200%	197%	168%	180%	166%	171%	
# 07 +	serum	22%	89%	86%	82%	84%	86%	83%	100%	5/3/2011
	IV bag	100%	111%	114%	110%	111%	114%	107%	120%	
# 08 +++	serum	0.27%	135%	130%	128%	125%	128%	131%	133%	3/28/2011
	IV bag	100%	96%	100%	99%	82%	86%	115%	62%	
#09 *	serum		Pt Dropped from Study	Failure to keep appointments						rescheduled 7/5/11
	IV bag									removed from study
# 10 *	serum		Pt dropped from study	Failure to keep appointments						
	IV bag									
#11 +++	serum	1.60%	117%	105%	106%	101%	102%	95%	99%	sched 6/21/11
	IV bag	100%	133%	114%	118%	114%	105%	133%	85%	
#12 *	serum		Pt dropped from study	Failure to keep appointments						resched 7/6/11
	IV bag									
#13 +++	serum	1%	94%	98%	96%	105%	98%	102%	100%	8/3/2011
	IV bag	100%	89%	93%	117%	97%	96%	104%	95%	
#14 ++	serum	5.60%	103%	87%	108%	98%	87%	84%	79%	8/19/2011
	IV bag	100%	62%	85%	74%	76%	72%	76%	22% ***	
Standard deviations *paired t-test*		0.07	0.34	0.41	0.49	0.46	0.42	0.40	0.56	
P value		*< .0001*	*0.9*	*0.55*	*0.75*	*0.66*	*0.77*	*0.36*	*0.39*	

** pt died due to CHF complications after completing 1st visit; not r/t study * Subjects removed from study for failure to maintain appointments
+ mild hemophilia A; ++ moderate hemophilia A; +++ severe hemophilia A *** Removed result from analysis due to improper processing

Results

Fourteen subjects agreed to participate; 4 failed to follow up,10 subjects were included in analysis; 7 severe, 2 moderate, and 1 mild;

Age range 26–62 years;

Ethnicity of subjects: 5 African American, 4 Caucasian, and 1 Hispanic.

The ranges of rFVIII-FS were 65–135% (blood) and 62-200% (bag).

Serum rFVIII-FS levels remained stable throughout the 8-hour time period despite decrease in rFVIII-FS levels in the IV bag consistent with previous rFVIII-FS continuous infusion studies.

After the start of infusion, there were no significant difference noted between the hourly rFVIII-FS levels in subjects and IV bag values (p-value range 0.36 to 0.9).

A total of 60 time points of cultures during the study, were negative.

All subjects tolerated the 8-hour infusion without reported adverse events or inhibitor development.

Conclusions

1. The alternative delivery method and safety of 8-hour continuous infusions of rFVIII-FS has been confirmed and well tolerated by all subjects.
2. This method can be helpful where mini-pumps are not available, allowing a standard safe delivery of rFVIII-FS continuous infusion by available means.

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