233-27

UPJOHN

CONFIDENTIAL

APR 2 2 1988

no ST

(Distribution outside the company in whole or in part requires written permission of Unit 9113 Manager.)

DIVISION OF MEDICAL AFFAIRS

Code No.: 9113-88-002
Protocol No.: M/9950/0006
Date Typed: March 28, 1988
Date Approved: March 28, 1988

TECHNICAL REPORT

TITLE: Stability of Various Concentrations of Methylprednisolone Sodium Succinate

AUTHOR: R. J. Townsend

ABSTRACT

The stability of SOLU-MEDROL® Sterile Powder (methylprednisolone sodium succinate) solutions has been investigated. After reconstitution, SOLU-MEDROL (2 grams, 1 gram, 500 mg, 250 mg, 125 mg, and 40 mg) were added to partial fill containers of 5% dextrose (D5) and 0.9% sodium chloride (NS) injection solutions. Additionally, 250 mg of SOLU-MEDROL was added to 1 liter containers of D5 and NS injection solutions. All solutions were stored at room temperature (25°C) under fluorescent lighting for the entire study. Samples from the above solutions were obtained and assayed at the time of preparation and at 12, 24, and 48 hours, and 7 days after preparation. All samples were assayed for 21-methylprednisolone hemisuccinate, 17-methylprednisolone hemisuccinate, and methylprednisolone alcohol. Additionally, all solutions were visually inspected for formation of haze or precipitate and the pH was determined at 0, 12, 24, 48 hours and 7 days. Results indicate no appreciable change in pH (-0.2 to -0.7 units), and no formation of haze or precipitate for 7 days. All solutions were stable (maintained at least 90% of original 21-methylprednisolone hemisuccinate concentration) for at least 48 hours after preparation.

John Bosso, Pharm.D., the University of Utah, Salt Lake City, Utah, was the study investigator. His attached final report will serve as the complete technical report for this study.

Stability of Various Concentrations of Reconstituted Methylprednisolone Sodium Succinate

FINAL REPORT

Introduction

The stability of SOLU-MEDROL® Sterile Powder (methylprednisolone sodium succinate) solutions has previously been investigated[1]. The duration of stability was noted to be dependent on concentration and diluent. Although all reconstituted and diluted solutions of SOLU-MEDROL Sterile Powder studied were noted to be chemically stable in D5W and NS for 24 hours, some of the solutions were judged instable due to the formation of a milky haze within a few hours.

Recently The Upjohn Company implemented a new process for manufacturing the bulk drug used in making the final SOLU-MEDROL Sterile Powder product. It is felt that this new processed bulk drug will result in a final product that will have greater durations of stability after reconstitution and dilution.

This study is designed to document the duration of stability of SOLU-MEDROL Sterile Powder after reconstitution and further dilution to various concentrations in 5% dextrose (D5) and 0.9% sodium chloride (NS) injection solutions.

Methods

SOLU-MEDROL Sterile Powder was reconstituted and diluted in the following solutions and volumes of dextrose 5% in water and normal saline:

2 grams in 50 ml glass bottles
1 gram in 50 ml glass bottles
0.5 gram in 50 ml glass bottles
0.25 gram in 50 ml glass bottles
0.25 gram in 1 L plastic bags
0.125 gram in 50 ml glass bottles
40 mg in 50 ml glass bottles

All solutions were prepared in duplicate. Samples from each container were assayed for 21-methylprednisolone hemisuccinate, 17-methylprednisolone hemisuccinate, and methylprednisolone alcohol in duplicate. Samples were obtained and assayed at the time of preparation and at 12, 24, and 48 hours, and 7 days after preparation

[1]Stability of Methylprednisolone Sodium Succinate in Small Volumes of 5% Dextrose and 0.9% Sodium Chloride Injections. R.J. Townsend, A.H. Puchala, S.L. Nail. American Journal Hospital Pharmacy; 1981, (38), 1319-1322.

Additionally, all containers were visually inspected for formation of haze or precipitate and the pH was determined at 0, 12, 24, 48 hours, and 7 days.

All solutions were stored at room temperature (approximately 25°C) under fluorescent lighting for the entire course of observation.

ASSAY

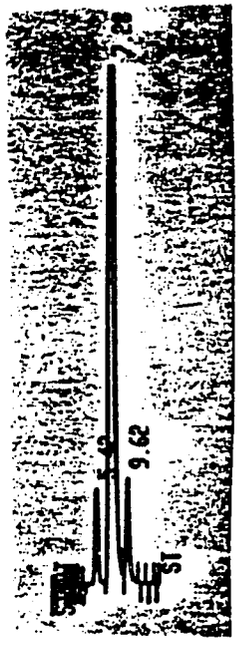
Mobile Phase (per liter)

A. 650 ml sodium acetate (0.05 M) adjusted to pH =5.4 with HCl
B. 350 ml acetonitrile (HPLC grade)
C. final pH adjusted to Ph = 5.4 with HCl
D. filtered and degased

Conditions

A. Column: Alltech C18, 10 micron
B. Flow rate: 1.2 ml/min
C. Detection wavelength = 248 nm
D. Injection volume = 5 mcl
E. AUFS: 1.0
F. Integrator chart speed: 0.1

SAMPLE CHROMATOGRAM



RETENTION TIMES

17-MHS : 5.42 min
21-MHS: 7.28 min
MPN alc: 9.62 min

Standard Curves

Standard curves for 21-methylprednisolone hemisuccinate, 17-methylprednisolone hemisuccinate and methylprednisolone alcohol were prepared seperately and validated. Seperate 21-methylprednisolone hemisuccinate standard curves reflecting high and low concentration ranges were prepared and validated.

1. 21-methylprednisolone hemisuccinate standard curve #1 (R = 0.9884897)

A. Intrarun Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
3.0	4	3.05	0.147	3.68
3.5	4	3.36	0.289	7.23
3.74	4	3.78	0.186	4.65
4.0	6	4.075	0.154	2.57
4.5	6	4.492	0.191	3.18

B. Day-to-day Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
2.0	4	2.17	0.123	5.67
3	5	3.16	0.131	4.15
3.5	5	3.52	0.121	3.44
3.75	5	3.77	0.107	2.84
4.0	5	4.16	0.178	4.28

2. 21-methylprednisolone hemisuccinate standard curve #2 (R = 0.9855590)

A. Intrarun Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
0.5	5	0.49	0.024	4.90
0.7	4	0.70	0.014	2.00
0.75	4	0.73	0.029	3.97
0.8	4	0.838	0.036	4.30
0.9	4	0.874	0.041	4.69

B. Day-to-day Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
0.2	5	0.207	0.0183	8.83
0.5	5	0.479	0.0331	6.91
0.7	5	0.704	0.0178	2.53
0.75	5	0.7498	0.0101	1.35
0.8	5	0.787	0.0326	4.14

3. 17-methylprednisolone hemisuccinate standard curve (R = 0.99750210)

A. Intrarun Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
0.15	5	0.146	0.0064	4.38
0.175	5	0.178	0.0092	5.17
0.188	5	0.189	0.0034	1.80
0.20	4	0.198	0.0043	2.17
0.225	5	0.226	0.0079	3.50

B. Day-to-day Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
0.15	5	0.142	0.0083	5.85
0.175	5	0.169	0.0123	7.28
0.188	4	0.184	0.00359	1.95
0.20	4	0.207	0.00896	4.33
0.225	5	0.229	0.00996	4.35

4. Methylprednisolone Alcohol standard curve (R = 0.993424344)

A. Intrarun Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
0.15	5	0.149	0.0011	0.74
0.175	5	0.173	0.004	2.31
0.188	4	0.191	0.005	2.62
2.0	5	0.200	0.005	2.50
0.225	5	0.222	0.0096	4.32

B. Day-to-day Validation

Nominal Concentration (mg/ml)	# Injections	Mean Concentration (mg/ml)	S.D.	C.V. (%)
0.15	5	0.149	0.0024	1.61
0.175	5	0.175	0.0023	1.31
0.188	5	0.185	0.0039	2.11
0.20	5	0.203	0.0055	2.71
0.225	5	0.221	0.0069	3.12

DILUTION SCHEME FOR ASSAYS (diluted with mobile phase)

Solution	Dilution
2 G/50ml	1:10
1 G/50ml	1:5
0.5G/50ml	2:5
0.25G/50ml	3:4
0.125G/50ml	1:3
40mg/50ml	none
0.25G/1L	none

RESULTS

Note on interpretation of results: concentrations below the lower end of the 17-methylprednisolone hemisuccinate and methylprednisolone alcohol (0.15 mg/ml) standard curves were considered to equal 0.

1. Concentrations of 21-methylprednisolone hemisuccinate at 5 sampling times: TABLE 1
2. Concentrations of 17-methylprednisolone hemisuccinate at 5 sampling times: TABLE 2
3. Concentrations of methylprednisolone alcohol at 5 sampling times: TABLE 3
4. Total concentrations for 3 components at 5 sampling times: TABLE 4
5. Mean percent changes in 21-methylprednisolone hemisuccinate from original concentration at 4 sampling times: TABLE 5
6. Mean percent changes in total of 3 components from original at 4 sampling times: TABLE 6
7. No evidence of haze or precipitate formation was observed in any solution at any time.
8. pH changes were observed in the range of -0.2 to -0.7 units over 7 days.

CONCLUSIONS

1. All solutions were stable (maintained at least 90% of original concentration) for at least 48 hours after preparation.
2. Solutions containing 0.25 Gm and 0.125 Gm in D5W and NS (50 ml) were stable for 7 days.

Methylprednisolone Stability Study Raw Data Summary TABLE 1

Solution	21-methylprednisolone hemisuccinate Concentration (mg/mL)				
	Original	12 hour	24 hour	48 hour	7 day
2 Gm/NS #1	30.42	29.99	29.90	29.52	23.59
2 Gm/NS #2	30.69	30.65	30.10	29.28	23.76
2 Gm/D5 #1	30.34	28.97	27.88	27.99	21.36
2 Gm/D5 #2	30.22	29.68	27.80	27.81	22.63
1 Gm/NS #1	15.55	16.43	15.56	17.28	12.84
1 Gm/NS #2	15.73	15.80	15.69	15.45	13.15
1 Gm/D5 #1	16.96	18.37	15.36	16.28	12.94
1 Gm/D5 #2	18.27	19.04	15.56	16.43	14.36
0.5 Gm/D5 #1	10.31	10.14	9.41	9.43	7.80
0.5 Gm/D5 #2	10.50	10.11	9.64	9.71	7.84
0.5 Gm/NS #1	11.54	11.30	11.24	11.13	9.08
0.5 Gm/NS #2	10.85	10.72	10.68	10.24	8.27
0.25G/NS #1	3.02	3.21	2.96	3.22	2.79
0.25G/NS #2	3.35	3.32	3.30	3.68	3.10
0.25G/D5 #1	3.11	2.92	2.95	3.04	2.81
0.25/D5 #2	3.17	2.89	3.09	2.81	3.05
0.125G/NS #1	1.86	1.85	1.80	1.95	1.84
0.125G/NS #2	1.83	1.80	1.79	1.97	1.86
0.125G/D5 #1	2.06	2.06	1.99	1.87	2.02
0.125G/D5 #2	2.07	2.00	1.97	1.80	1.80
40mg/NS #1	0.819	0.884	0.884	0.812	0.722
40mg/NS #2	0.835	0.818	0.799	0.74	0.66
40mg/D5 #1	0.889	0.883	0.861	0.802	0.692
40mg/D5 #2	0.848	0.829	0.82	0.762	0.654
250mg/NS #1	0.335	0.331	0.302	0.381	0.293
250mg/NS #2	0.302	0.305	0.302	0.285	0.284
250mg/D5 #1	0.317	0.318	0.315	0.306	0.301
250mg/D5 #2	0.307	0.307	0.306	0.296	0.293

Note: Last 4 solutions prepared in 1 liter bags; all previous solutions in 50 ml glass bottles.

Methylprednisolone Stability Study Raw Data Summary TABLE 2

Solution	17-methylprednisolone hemisuccinate Concentration (mg/mL)				
	Original	12 hour	24 hour	48 hour	7 day
2 Gm/NS #1	0.47	0.34	0.93	1.59	0.74
2 Gm/NS #2	0.46	0.60	1.01	1.84	0.55
2 Gm/D5 #1	0.50	0.70	1.09	2.03	0.62
2 Gm/D5 #2	0.52	0.54	1.05	1.78	0.37
1 Gm/NS #1	0.41	0.38	0.61	0.79	0.00
1 Gm/NS #2	0.43	0.39	0.62	0.86	0.00
1 Gm/D5 #1	0.00	0.00	0.35	0.75	0.91
1 Gm/D5 #2	0.00	0.00	0.35	0.67	1.03
0.5 Gm/D5 #1	0.00	0.00	0.20	0.36	0.60
0.5 Gm/D5 #2	0.00	0.00	0.19	0.35	0.28
0.5 Gm/NS #1	0.00	0.00	0.18	0.34	0.57
0.5 Gm/NS #2	0.00	0.00	0.18	0.29	0.58
0.25G/NS #1	0.00	0.00	0.00	0.00	0.26
0.25G/NS #2	0.00	0.00	0.00	0.15	0.29
0.25G/D5 #1	0.00	0.00	0.00	0.00	0.27
0.25G/D5 #2	0.00	0.00	0.00	0.15	0.28
0.125G/NS#1	0.00	0.00	0.00	0.00	0.00
0.125G/NS#2	0.00	0.00	0.00	0.00	0.00
0.125G/D5#1	0.00	0.00	0.00	0.00	0.00
0.125G/D5#2	0.00	0.00	0.00	0.00	0.00
40mg/NS#1	0.00	0.00	0.00	0.00	0.00
40mg/NS#2	0.00	0.00	0.00	0.00	0.00
40mg/D5#1	0.00	0.00	0.00	0.00	0.00
40mg/D5#2	0.00	0.00	0.00	0.00	0.00
250mg/NS#1	0.00	0.00	0.00	0.00	0.00
250mg/NS#2	0.00	0.00	0.00	0.00	0.00
250mg/D5#1	0.00	0.00	0.00	0.00	0.00
250mg/D5#2	0.00	0.00	0.00	0.00	0.00

Note: Last 4 solutions prepared in 1 liter bags; all previous solutions in 50 ml glass bottles.

Methylprednisolone Stability Study Raw Data Summary TABLE 3

Solution	17-methylprednisolone alcohol Concentration (mg/mL)				
	Original	12 hour	24 hour	48 hour	7 day
2 Gm/NS #1	0.00	0.64	1.46	1.63	1.59
2 Gm/NS #2	0.00	0.60	1.46	1.64	1.70
2 Gm/D5 #1	0.00	0.70	1.51	1.77	1.51
2 Gm/D5 #2	0.00	0.54	1.51	1.71	1.65
1 Gm/NS #1	0.00	0.38	0.77	0.84	0.90
1 Gm/NS #2	0.00	0.39	0.78	0.85	0.95
1 Gm/D5 #1	0.60	0.66	0.71	0.81	0.92
1 Gm/D5 #2	0.60	0.65	0.72	0.79	0.97
0.5 Gm/D5 #1	0.29	0.32	0.35	0.38	0.49
0.5 Gm/D5 #2	0.30	0.32	0.35	0.39	0.48
0.5 Gm/NS #1	0.30	0.32	0.34	0.37	0.46
0.5 Gm/NS #2	0.30	0.32	0.34	0.36	0.46
0.25G/NS #1	0.16	0.17	0.19	0.18	0.23
0.25G/NS #2	0.16	0.17	0.18	0.21	0.26
0.25G/D5 #1	0.16	0.17	0.18	0.21	0.27
0.25G/D5 #2	0.16	0.17	0.18	0.21	0.26
0.125G/NS #1	0.00	0.00	0.00	0.00	0.00
0.125G/NS #2	0.00	0 00	0.00	0.00	0.00
0.125G/D5 #1	0.00	0.00	0.00	0.00	0.00
0.125G/D5 #2	0.00	0.00	0.00	0.00	0.00
40mg/NS #1	0.00	0.00	0.00	0.00	0.00
40mg/NS #2	0.00	0.00	0.00	0.00	0.00
40mg/D5 #1	0.00	0.00	0.00	0.00	0.00
40mg/D5 #2	0.00	0.00	0.00	0.00	0.00
250mg/NS #1	0.00	0.00	0.00	0.00	0.00
250mg/NS #2	0.00	0.00	0.00	0.00	0.00
250mg/D5 #1	0.00	0.00	0.00	0.00	0.00
250mg/D5 #2	0.00	0.00	0.00	0.00	0.00

Note: Last 4 solutions prepared in 1 liter bags; all previous solutions in 50 ml glass bottles.

Methylprednisolone Stability Study Raw Data Summary TABLE 4

Total Concentrations (21-hemisuccinate + 17-hemisuccinate + alcohol)

Solution	Concentration (mg/mL)				
	Original	12 hour	24 hour	48 hour	7 day
2 Gm/NS #1	30.89	30.97	32.29	32.74	25.92
2 Gm/NS #2	31.15	31.85	32.57	32.76	26.01
2 Gm/D5 #1	30.84	30.37	30.48	31.79	23.49
2 Gm/D5 #2	30.74	30.76	30.36	31.30	24.65
1 Gm/NS #1	15.96	17.19	16.94	18.91	13.74
1 Gm/NS #2	16.16	16.58	17.09	17.16	14.10
1 Gm/D5 #1	17.56	19.03	16.42	17.84	14.77
1 Gm/D5 #2	18.57	19.69	16.63	17.89	14.45
0.5 Gm/D5 #1	10.60	10.46	9.96	10.17	8.89
0.5 Gm/D5 #2	10.80	10.42	10.18	10.45	8.60
0.5 Gm/NS #1	11.84	11.62	11.76	11.84	10.11
0.5 Gm/NS #2	11.15	11.07	11.00	10.89	9.31
0.25G/NS #1	3.18	3.38	3.15	3.40	3.28
0.25G/NS #2	3.51	3.49	3.48	4.04	3.62
0.25G/D5 #1	3.27	3.09	3.13	3.25	3.35
0.25G/NS #2	3.31	3.06	3.27	3.17	3.59
0.125G/NS #1	1.86	1.85	1.80	1.95	1.84
0.125G/NS #2	1.83	1.80	1.79	1.97	1.86
0.125G/D5 #1	2.06	2.06	1.99	1.87	2.02
0.125G/D5 #2	2.07	2.00	1.97	1.80	1.80
40mg/NS #1	0.819	0.884	0.884	0.812	0.722
40mg/NS #2	0.835	0.818	0.799	0.74	0.66
40mg/D5 #1	0.889	0.883	0.861	0.802	0.692
40mg/D5 #2	0.848	0.829	0.82	0.762	0.654
250mg/NS #1	0.335	0.331	0.302	0.381	0.293
250mg/NS #2	0.302	0.305	0.302	0.285	0.284
250mg/D5 #1	0.317	0.318	0.315	0.306	0.301
250mg/D5 #2	0.307	0.307	0.306	0.296	0.293

Note: Last 4 solutions prepared in 1 liter bags, all previous solutions in 50 ml glass bottles

Methylprednisolone Stability Study Raw Data Summary TABLE 5

MEAN PERCENT CHANGES FROM ORIGINAL CONCENTRATION

21-hemisuccinate only

	12 hour	24 hour	48 hour	7 day
2 Gm/NS	-0.77	-1.82	-4.28	-22.52
2 Gm/D5	-3.6	-8.06	-7.86	-27.36
1 Gm/NS	-3.06	-0.09	-1.78	-16.92
1 Gm/D5	6.26	-9.43	-7.07	-22.55
0.5 Gm/D5	-2.68	-8.46	-8.03	-24.84
0.5 Gm/NS	-1.64	-2.09	-4.59	-22.55
0.25 Gm/NS	2.7	-1.74	8.24	- 7.54
0.25 Gm/D5	-7.95	-3.83	-6.81	- 6.72
0.125 Gm/NS	-1.04	-2.17	5.16	0.27
0.125 Gm/D5	-1.69	-4.12	-9.22	- 7.49
0.04 Gm/NS	2.95	1.82	-6.12	-13.35
0.04 Gm/D5	-1.46	-4.41	-9.97	-22.52
250mg/NS	-0.1	-4.93	-5.3	- 9.44
250mg/D5	0.16	-0.5	-3.21	- 4.81

Note: Last two solutions prepared in 1 liter bags; all previous solutions in 50 ml glass bottles.

Methylprednisolone Stability Study Raw Data Summary TABLE 6

MEAN PERCENT CHANGES FROM ORIGINAL CONCENTRATION

21-hemisuccinate + 17-hemisuccinate + alcohol

	12 hour	24 hour	48 hour	7 day
2 Gm/NS	1.26	4.55	5.58	-16.30
2 Gm/D5	-0.73	-1.21	-2.45	-21.82
1 Gm/NS	5.16	5.95	12.34	-13.33
1 Gm/D5	7.20	8.47	-0.89	-19.04
0.5 Gm/D5	-2.42	-5.89	-3.65	-18.25
0.5 Gm/NS	-1.29	-1.02	-1.17	-15.56
0.25 Gm/NS	2.86	-0.90	11.01	-3.14
0.25 Gm/D5	-6.53	-2.75	-6.68	-5.46
0.125 GM/NS	-1.04	-2.17	5.16	0.27
0.125 Gm/D5	-1.69	-4.12	-9.22	- 7.49
0.04 Gm/NS	2.95	1.82	-6.12	-13.35
0.04 Gm/D5	-1.46	-4.41	-9.97	-22.52
25mg/NS	-0.1	-4.93	-5.3	-9.44
250mg/D5	0.16	-0.5	-3.21	-4.81

Note: Last two solutions prepared in 1 liters bags; all previous solutions in 50 ml glass bottles.

StabStudy/ard

INDEXING AND REFERENCE PAGE

U-numbers:

KEY WORDS:

Stability
Compatibility
Methylprednisolone sodium succinate
21-methylprednisolone hemisuccinate
17-methylprednisolone hemisuccinate
Methylprednisolone alcohol

Trade Names and/or Generic Chemical Names:

SOLU-MEDROL® Sterile Powder	Methylprednisolone sodium succinate