COMPATIBILITY AND STABILITY OF HYOSCINE N-BUTYL BROMIDE AND FUROSEMIDE ADMIXTURES FOR USE IN PALLIATIVE CARE

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20th Congress of eahp
Hamburg 25-27 March 2015
PP-002

BACKGROUND

In order to avoid separate injections, admixtures of drugs are frequently used in palliative care settings. There are different factors that can influence the compatibility and stability of the mixture: drug type, concentration, solvent, container, temperature and light. There are some mixtures of drugs with proven stability, but there is lack of evidence about the stability and compatibility of the combination of hyoscine N-butyl bromide and furosemide

PURPOSE

To evaluate the compatibility and stability of three admixtures of hyoscine N-butyl bromide and furosemide at different concentration and at two temperatures (25ºC and 37ºC) in NaCl 0.9% stored in elastomeric infusors protected from light

MATERIAL AND METHODS

- Hyoscine N-butyl bromide Boehringer Ingelheim
- Furosemide Fresenius Kabi
- NaCl 0.9% sterile solution
- Portable Elastomeric Infusion System Baxter
- Agilent 1220 Infinity LC System
- Column: Zorbax Eclipse XDB-C18, 4.6 x 250 mm (5 µm)
- Mobile phase: acetonitrile-water 80:20 (v/v)
- Flow rate 1.5 mL/min; λ= 220 nm
- Bacteriological and culture oven, Selecta (INCUDIGIT 19L 2001246)

The samples were prepared and diluted in NaCl 0.9% in elastomeric infusor in triplicate to obtain six different conditions of concentration and/or temperature of storage (concentration: 2.0 mg/mL–2.0 mg/mL, 1.0 mg/mL–0.6 mg/mL and 0.6 mg/mL–0.6 mg/mL of hyoscine N-butyl bromide and furosemide respectively; temperature 25ºC and 37ºC).

The concentration of admixture drugs was periodically determined using a HPLC-UV method by interpolation from the calibration curves prepared at (0, 1, 2, 3, 7, 11, 15) days from the standards. Mixtures were considered stable if there was less than 10% degradation.

Also, the drug mixtures were examined for signs of precipitation or turbidity and gas production under a bright light against a dark background.

We conducted a forced degradation study to validate our method.

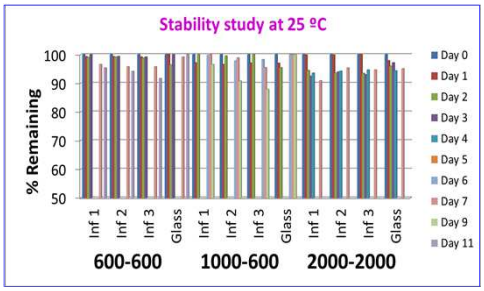
RESULTS

Chemical stability

25 ºC [Admixture] ± SD* (mg/L)

600-600 mg/L					1000-600 mg/L					2000-2000 mg/L				
Day	Inf 1	Inf 2	Inf 3	Glass	Day	Inf 1	Inf 2	Inf 3	Glass	Day	Inf 1	Inf 2	Inf 3	Glass
0	120	120	120	120	0	160	160	160	160	0	180	180	180	180
1	119.2±1.4	119,2±1.4	119.0±0.8	120.1±1.1	1	155.4±4.4	154.5±2.3	155.4±1.8	155.2±1.0	1	179.8±1.8	179.9±1.1	181.6±1.1	176.3±0.1
2	118.8±3.6	119.0±1.6	118.5±0.4	115.8±3.2	2	166.4±1.9	159.4±2.5	161.2±1.9	152.8±2.7	2	177.9±2.2	175.9±1.1	175.9±1.0	172.8±0.8
3	120.3±0.8	119.3±1.4	119.0±0.9	120.0±1.9	6	159.6±2.8	156.5±1.7	157.3±3.0	166.0±4.8	3	179.2±0.8	177.1±1.0	167.4±1.7	175.0±0.3
7	115.9±0.5	115.0±1.6	115.0±1.1	119.0±0.8	7	164.6±2.2	158.2±2.1	152.8±1.9	165.5±1.1	4	168.4±1.3	169.8±0.5	170.4±0.8	169.9±1.0
11	114.5±1.7	113.0±0.8	110.0±0.4	120.1±0.9	9	150.3±3.0	145.3±4.2	140.7±3.2	154.6±2.2	7	163.7±0.2	171.7±0.6	170.5±1.3	171.2±0.7

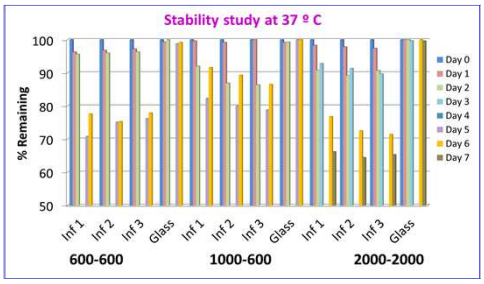
* Mean ± Standard deviation; n=4



37 ºC [Admixture] ± SD* (mg/L)

	600-600 mg/L				1000-600 mg/L				2000-2000 mg/L				
Day	Inf 1	Inf 2	Inf 3	Glass	Day	Inf 1	Inf 2	Inf 3	Glass	Day	Inf 1	Inf 2	Inf 3	Glass
0	120	120	120	120	0	160	160	160	160	0	180	180	180	180
1	115.5±0.4	116.1±0.3	116.6±0.6	119.2±0.3	1	159.4±1.2	158.7±1.3	160.0±1.0	158.7±2.1	1	177.0±2.4	176.1±1.1	175.3±2.1	180.0±1.8
2	114.7±0.3	115.2±2.4	115.6±1.4	120.0±0.2	2	147.2±0.3	139.0±0.4	138.2±0.3	158.9±1.2	2	163.5±1.2	160.5±2.5	163.2±2.3	181.8±1.9
5	85.0±0.9	90.1±0.3	91.4±1.4	118.6±0.3	5	131.6±0.9	128.0±0.5	126.1±1.3	160.0±1.0	3	167.0±0.7	162.4±1.5	161.4±3.2	179.5±1.5
6	93.1±0.2	90.3±0.4	93.5±0.2	119.0±0.3	6	146.±1.1	142.9±1.0	138.4±2.0	160.0±0.6	6	138.3±1.4	130.5±2.3	128.6±3.4	180.3±1.0
										7	119.1±0.6	115.9±2.2	117.6±3.0	179.2±1.5

* Mean ± Standard deviation; n=4



Physical stability

All solutions were initially clear and colourless and remained so for the duration of the study. Visible particles appear in the infusors at the same time that decrease the concentration of the admixture stored into they

FORCED DEGRADATION STUDIES

500 µL admixture 160 mg/L (80-80)

100 µL
200 µL
300 µL
500 µL
1000 µL

- HCl (1 M, 0.1 M)
- NaOH (1 M, 0.1 M)
- NaClO (2 M, 0.2 M)
- H_2O_2 (3 %, 10%)
- Temperature (40ºC, 60ºC, 80ºC)
- UV radiation

- Additions of HCl, NaOH have not influence about the chromatographic signal. The area diminishes by dilution effects when the amount of degradant is higher and also the signal is constant with the time. With NaOH 1 M appears other signal at Rt = 3.5 min
- Temperature has not influence
- After one day under UV radiation, the signal of the admixture diminishes and also colour change is observed into glass
- Additions of NaClO 2 M, and H_2O_2 (3%, 10%) increase the chromatographic signal and stay constant with the time

Stability of admixtures

Hyoscine N-butyl bromide-furosemide (mg/L-mg/L)	Days 25 ºC	37 ºC
600-600	12	3
1000-600	8	2
2000-2000	8	2

CONCLUSIONS

The admixture of hyoscine N-butyl bromide and furosemide in NaCl 0.9% in elastomeric infusor can be safely used in palliative care.

It can be prepared in advance and stored at room temperature for at least 8 days, but the infusion with a system worn close to a patient that may reach a temperature closer to 37ºC cannot be longer than two days.