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Notes

Compatibility of granisetron towards glass and plastics and its stability under various storage conditions

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Abstract

We evaluated the compatibility of granisetron as an undiluted solution for injection, and diluted in 5% glucose or 0.9% NaCl, towards glass, polypropylene and PVC containers over a period of 15 days. The solutions were exposed to various temperature and light conditions. The granisetron was analysed by high-performance liquid chromatography. The results show that undiluted granisetron was stable in polypropylene syringes during the 15-day period under all the storage conditions tested, i.e., light and ambient temperature, dark and ambient temperature, refrigeration at 4°C. In contrast, variations in concentration were observed over time when the drug was diluted in 5% glucose or 0.9% NaCl irrespective of the container or the storage conditions. While undiluted granisetron at 1 mg/ml may be safely kept in polypropylene syringes, dilutions in 5% glucose or 0.9% NaCl should therefore be made up extemporaneously. © 1997 Elsevier Science B.V.

Keywords: Granisetron; Compatibility; Stability; Biomaterials; Conservation

1. Introduction

Granisetron is a selective 5-HT3 receptor antagonist. It has proved effective in the prevention and treatment of vomiting induced by cytostatics. In

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clinical practice it is administered by slow intravenous injection or intravenous infusion after dilution in a solution such as 5% glucose or 0.9% NaCl. Unlike that of the related drug ondansetron (Bosso et al., 1992; Graham et al., 1992; Stiles et al., 1992; Jhee et al., 1993; Casto, 1994), the stability of diluted granisetron during storage has not been thoroughly studied (Chung et al., 1995).

The purpose of the work reported here was to evaluate (i) the compatibility of granisetron towards the various materials used in the syringes, bottles and bags it may be contained in (glass, polypropylene, polyvinylchloride), (ii) its stability, undiluted and in 5% glucose or 0.9% NaCl, and (iii) its behavior under different conditions of light and temperature, to determine optimal storage conditions.

Stability was studied by monitoring the concentration of granisetron for 15 days under each combination of conditions (container, dilution, light, temperature).

2. Materials and methods

2.1. Drugs

Granisetron is marketed by Smithkline-Beecham under the proprietary name Kytril®. We used 3-ml vials containing 3 mg of granisetron.

2.2. Solvents for dilution and containers

The dilution solvents used were: 5% glucose and 0.9% NaCl in glass bottles (Braun) and PVC bags (Viaflex®, Aguettant). We also used polypropylene syringes (Plastipack®, Becton Dickinson)

2.3. Chromatography

The granisetron was assayed by high-performance liquid chromatography using the following instrumentation (Merck–Hitachi); an L5000 LC Gradient Controller, a 655-A liquid chromatograph pump, a Rheodyne 7161 with a 20-μl injection loop, an L 4250 UV-Visible detector and a D2000 chromatointegrator. The column was a type C18 Lichrosphere RP 18 (5 μm, 125 × 4 mm ID (Merck)).

The internal standard (ondansetron) was supplied by Glaxo.

The mobile phase was a 30/70 v/v mixture of 0.05 mol/l, pH 5.6 phosphate buffer and acetonitrile. The flow rate of the mobile phase was 1.2 ml/min.

The detection wavelength was 216 nm.

The standard solutions were prepared by dilution in water of stock solutions of 1 mg/ml granisetron and 2 mg/ml ondansetron (internal standard), to obtain granisetron concentrations of 5, 10, 20 and 40 μg ml for a set concentration of ondansetron of 10 μg/ml. These solutions were used to plot a calibration line with equation $y = ax + b$ (where x = granisetron concentration and y = ratio of areas under the granisetron peak and under the ondansetron peak). Granisetron concentrations in experimental samples were obtained by extrapolation from this graph.

The chromatography method used was validated specifically to study the stability of the granisetron. It had to be able to detect and separate granisetron from any degradation products. Accordingly, we carried out a deliberate complete degradation of the drug molecule by means of large pH changes and strong heating. The solution obtained was then analysed by chromatography to check there was no interference of degradation products with the granisetron.

2.4. Stability study design

We evaluated the stability of granisetron under various storage conditions commonly encountered in clinical practice. The drug studied can be administered directly in a solution through a perfusion set. In this case it is prepared beforehand undiluted in a polypropylene syringe, and so its concentration is that of the commercial solution, i.e. 1 mg/ml. It can also be diluted, usually in 5% glucose or 0.9% NaCl. The recommended dosage is one vial in 125 ml of solvent, which corresponds to a theoretical concentration of 24 μg/ml. We studied the stability of granisetron after dilution in 5% glucose and 0.9% NaCl in glass vials and PVC bags.

Table 1
Study of the stability of granisetron: experimental conditions

Container	Solvent for dilution	Concentration of granisetron	Condition of storage	No. of preparations
Polypropylene syringe	No solvent	1 mg/ml	Ambient light and temperature	3
			Dark and ambient temperature	3
			Refrigerated at +4°C	3
Glass bottle	5% glucose	24 μg/ml	Ambient light and temperature	3
			Dark and ambient temperature	3
			Refrigerated at +4°C	3
	O.9% NaCl	24 μg/ml	Ambient light and temperature	3
			Dark and ambient temperature	3
			Refrigerated at +4°C	3
PVC bag	5% glucose	24 μg/ml	Ambient light and temperature	3
			Dark and ambient temperature	3
			Refrigerated at +4°C	3
	O.9% NaCl	24 μg/ml	Ambient light and temperature	3
			Dark and ambient temperature	3
			Refrigerated at +4°C	3

The different solutions of granisetron made up in bottles, bags and syringes were submitted to the following storage conditions. For polypropylene containers (syringes), nine preparations of granisetron at 1 mg/ml were made up. Of these nine preparations, three were kept at room temperature and ambient light, three at ambient temperature and in darkness, and three refrigerated at 4°C. For each other container (glass and PVC), 18 preparations of granisetron at 24 μg/ml were made up: nine were diluted with 5% glucose and nine with 0.9% NaCl. Of each group of nine preparations, three were kept at room temperature and ambient light, three at ambient temperature and in darkness, and three refrigerated at 4°C.

A first sample of each preparation was taken immediately after dilution and filling, and the granisetron concentration obtained served as reference (TO). Samples were subsequently taken at the following times; 1, 2, 4, 6 h on Day 1, and then on Days 2, 3, 4, 5, 8 and 15.

The experimental conditions of the stability study are described in Table 1.

2.5. Computations and statistical analysis

Means were calculated for the three values obtained at each sample time for each container material, dilution solvent and storage condition. The mean granisetron concentrations were then expressed in percent of the initial concentration at TO (100%).

To test for significant differences according to materials, solvents and storage conditions, the results obtained were analysed statistically by multiple analysis of variance, including one factor repeated in time followed by a posteriori multiple comparisons (Neumann-Keuls). The significance threshold was 0.05.

3. Results and discussion

3.1. Chromatography

The granisetron assay method was validated. Its precision (intra-day and inter-day variabilities) was satisfactory, with coefficients of variation $< 6\%$ ($n = 10$).

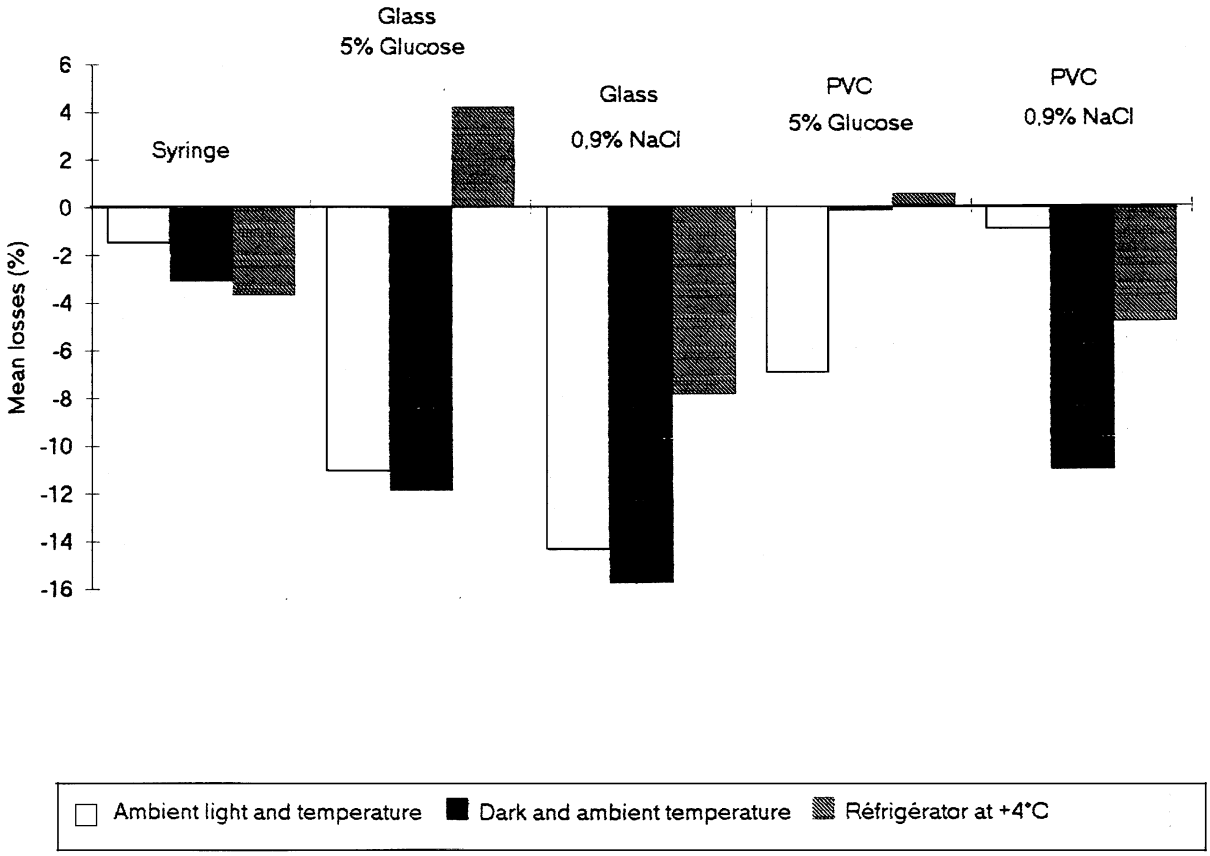

Fig. 1. Mean variations in granisetron concentration over 15 days.

The method displayed high linearity in the concentration range 5–40 ng/ml with a correlation coefficient $r = 0.9997$ ($r^2 = 0.9994$). The equation for the mean calibration plot was $y = 8.82 \times 10^{-2}x + 1.30 \times 10^{4}$.

The chromatography method was validated as an analytical method for the stability study. It provided specific quantitation of the drug itself (granisetron) without interference by any of its breakdown products.

3.2. Stability of granisetron in polypropylene syringes

The results of the study are shown in Table 2.

We observed no significant variation in the concentration of granisetron over time ($p = 0.135$); after 15 days storage in the polypropylene syringes, the granisetron concentrations varied by no more than 10% of the initial concentration observed at TO, regardless of the storage conditions. Overall, the light and temperature had no influence on the stability of granisetron in polypropylene syringes at 1 mg/ml ($p = 0.579$)

3.3. Stability of granisetron in glass bottles and PVC bags

The results of the granisetron stability study for glass and PVC containers (after dilution in 5% glucose and 0.9% NaCl), are shown in Table 3 and Table 4, respectively.

The results obtained were comparable regardless of the container material (glass and PVC). We observed no significant difference in the concentrations of granisetron according to the storage conditions ($p = 0.077$ for glass and $p = 0.193$ for PVC). The physical and chemical stability of

Table 2
Stability of granisetron in polypropylene syringes

	Actual initial concentration, mg/ml (mean ± SD)	% initial concentration remaining after storage (mean ± SD)									
		1 h	2 h	4 h	6 h	1 day	2 days	3 days	4 days	8 days	15 days
Ambient light and temperature	1.06 ± 0.14	104.8 ± 19.2	108.9 ± 19.6	93.3 ± 9.5	98.5 ± 5.6	94.7 ± 21.4	96.7 ± 13.8	94.5 ± 12.6	99.5 ± 9.5	105.6 ± 15.8	98.9 ± 14.0
Dark and ambient temperature	1.07 ± 0.11	98.5 ± 5.4	94.8 ± 2.3	98.2 ± 7.8	96.0 ± 12.5	92.4 ± 12.5	95.2 ± 3.2	92.0 ± 4.3	99.2 ± 6.0	103.5 ± 12.6	99.0 ± 6.1
Refrigerated at 4°C	0.97 ± 0.03	108.3 ± 2.2	106.7 ± 1.8	107.6 ± 1.8	105.1 ± 6.4	103.1 ± 2.0	100.8 ± 7.2	104.9 ± 3.4	105.2 ± 0.9	100.7 ± 4.2	94.3 ± 9.9

Table 3
Stability of granisetron in glass bottles after dilution in 5% glucose or in 0.9% NaCl5% glucose

	Actual initial concentration, μg/ml (mean ± SD)	% initial concentration remaining after storage (mean ± SD)									
		1 h	2 h	4 h	6 h	1 day	2 days	3 days	4 days	8 days	15 days
5% glucose											
Ambient light and temperature	28.6 ± 0.7	89.7 ± 9.6	93.3 ± 4.2	95.7 ± 22.7	82.9 ± 13.0	84.3 ± 2.3	84.3 ± 9.8	85.9 ± 1.0	81.1 ± 0.4	92.9 ± 12.4	99.4 ± 26.3
Dark and ambient temperature	27.6 ± 3.0	92.3 ± 4.0	89.7 ± 9.8	93.4 ± 4.5	90.1 ± 2.0	90.5 ± 3.2	81.8 ± 9.8	87.5 ± 3.1	86.1 ± 6.2	84.7 ± 15.9	85.2 ± 21.3
Refrigerated at 4°C	22.9 ± 0.9	104.0 ± 6.4	107.1 ± 4.9	108.9 ± 0.1	100.8 ± 9.5	98.2 ± 17.5	110.0 ± 4.8	107.0 ± 7.5	104.7 ± 2.5	98.4 ± 9.2	102.5 ± 1.5
0.9% NaCl											
Ambient light and temperature	29.5 ± 5.3	90.6 ± 15.9	88.1 ± 12.4	87.4 ± 12.6	93.8 ± 3.4	87.6 ± 13.0	80.8 ± 14.0	81.0 ± 16.1	82.1 ± 11.3	80.0 ± 13.1	84.8 ± 14.4
Dark and ambient temperature	29.8 ± 6.0	88.8 ± 17.3	83.7 ± 16.3	86.5 ± 12.2	87.9 ± 16.4	85.2 ± 14.0	79.9 ± 17.6	81.5 ± 14.5	82.1 ± 13.8	81.9 ± 16.8	84.3 ± 12.5
Refrigerated at 4°C	26.6 ± 1.8	94.8 ± 9.6	93.1 ± 8.4	91.4 ± 7.3	89.6 ± 6.7	98.1 ± 8.7	93.9 ± 8.4	91.1 ± 9.8	86.1 ± 7.2	93.1 ± 11.4	90.9 ± 7.9

Table 4
Stability of granisetron in PVC bags after dilution in 5% glucose and in 0.9% NaCl

	Actual initial concentration, μg/ml (mean ± SD)	% initial concentration remaining after storage (mean ± SD)									
		1 h	2 h	4 h	6 h	1 day	2 days	3 days	4 days	8 days	15 days
5% glucose											
Ambient light and temperature	25.4 ± 1.6	94.7 ± 5.9	92.8 ± 6.5	94.8 ± 6.5	89.6 ± 11.7	99.1 ± 13.2	91.7 ± 6.7	92.1 ± 8.8	87.0 ± 8.8	94.1 ± 12.6	93.9 ± 16.7
Dark and ambient temperature	23.5 ± 1.8	108.9 ± 13.1	103.2 ± 6.4	100.2 ± 2.7	97.7 ± 5.0	103.3 ± 4.2	91.9 ± 5.8	93.8 ± 9.4	97.0 ± 6.9	97.5 ± 18.9	104.1 ± 21.0
Refrigerated at 4°C	24.6 ± 2.4	100.0 ± 0.5	103.2 ± 10.1	99.9 ± 7.5	101.3 ± 6.5	101.1 ± 7.9	101.5 ± 9.3	104.1 ± 5.3	98.0 ± 4.9	97.1 ± 9.6	99.1 ± 6.3
0.9% NaCl											
Ambient light and temperature	22.4 ± 0.2	101.2 ± 7.1	101.9 ± 0.9	101.1 ± 2.7	98.5 ± 0.5	98.3 ± 2.2	100.9 ± 5.5	97.8 ± 5.8	90.7 ± 2.6	101.8 ± 8.2	97.5 ± 2.2
Dark and ambient temperature	25.1 ± 1.5	97.3 ± 7.1	92.4 ± 4.5	89.8 ± 5.1	89.4 ± 3.8	88.8 ± 5.1	89.1 ± 4.5	84.7 ± 3.5	82.0 ± 8.2	89.7 ± 6.3	86.2 ± 5.9
Refrigerated at 4°C	22.5 ± 0.7	97.2 ± 1.0	99.9 ± 0.2	94.7 ± 0.7	101.3 ± 5.4	95.6 ± 1.5	97.2 ± 1.7	91.3 ± 0.7	85.7 ± 1.3	96.4 ± 5.1	92.3 ± 1.3

granisetron was unaffected by the light and temperature differences.

The granisetron concentration did not differ significantly according to the dilution solvent (5% glucose or 0.9% NaCl) ($p = 0.162$ for glass and $p = 0.539$ for PVC).

In contrast, we observed a significant variation in the granisetron concentration in time ($p < 0.0001$ for the two materials). However, it cannot be asserted that these variations resulted from an actual loss of drug over time, since chromatography revealed no degradation products, and since the concentration of granisetron did not decline regularly, but sometimes oscillated about the initial concentration at TO.

3.4. Mean variations in granisetron concentration over 15 days

The variations are expressed in percent relative to the concentration recorded at TO (0%), and are shown in Fig. 1.

This calculation of the mean variation in granisetron concentration during 15 days storage confirms a marked fall in granisetron concentration after dilution in PVC and glass containers. In contrast, the variations were only slight in the syringe (less than 4% loss).

4. Conclusion

The results show that granisetron is stable in polypropylene syringes irrespective of the storage conditions tested. However, its stability may be slightly impaired on dilution in 5% glucose or 0.9% NaCl. Consequently, granisetron should preferably be stored undiluted (at 1 mg/ml) in polypropylene syringes and diluted extemporaneously in 5% glucose or 0.9% NaCl as required. This is indeed the commonest procedure in clinical practice. We should add that this study did not consider sterility and only evaluates the chemical stability of the drug solutions.

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