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Compatibility of Tropisetron with Glass and Plastics. Stability under Different Storage Conditions

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Abstract

The compatibility of tropisetron (pure undiluted 1 mg mL^{-1} and diluted with 5% glucose or 0·9% NaCl (saline)) with glass, poly(vinyl chloride), polypropylene or polyethylene containers has been studied over a period of two weeks. The drug solutions were exposed to different light and temperature conditions. Tropisetron was assayed by high-performance liquid chromatography.

The results show that undiluted tropisetron is stable in polypropylene syringes for two weeks under all the storage conditions tested (daylight at room temperature, dark at room temperature, refrigerator at 4°C). Some variations in concentration were observed after dilution of tropisetron but these remained within 10% of the initial concentration. Tropisetron can be stored undiluted at 1 mg mL^{-1} in polypropylene syringes, although it is preferable to perform dilutions extemporaneously. Tropisetron diluted with 5% glucose or saline can be kept equally well in glass, poly(vinyl chloride) (Travenol bags) or polyethylene (ecoflac) containers.

Since the early 1990s several medical drugs in the anti-$5HT_3$ class have been commercialized. The latest on the market is tropisetron (navoban) supplied by Sandoz. It is prescribed for the treatment of nausea and vomiting induced by cytostatic chemotherapy or radiotherapy and so improves the quality of life of patients undergoing anti-cancer treatment (Lee et al 1993; Falkson & Falkson 1995). The product is administered immediately after chemotherapy by either perfusion or direct intravenous injection.

The stability of tropisetron has not been extensively studied, unlike that of the related drugs ondansetron (Bosso et al 1992; Graham et al 1992; Stiles et al 1992; Jhee et al 1993; Casto 1994) and granisetron (Chung et al 1995). The purpose of this study was to evaluate the compatibility of tropisetron and the various materials used in perfusion sets (bags, bottles, syringes), and its stability after dilution with different solvents. In parallel, the stability of tropisetron when stored under different light and temperature conditions was also studied.

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Materials and Methods

Test product

Sandoz supplies tropisetron (navoban) as an injectable solution in 5 mL vials containing 5 mg tropisetron base.

Solvents for dilution, and containers

Tropisetron can be diluted with 5% glucose or 0·9% sodium chloride (saline). These solvents are supplied in soda-glass bottles (B. Braun Medical), poly(vinyl chloride) bags (Travenol, Baxter) or polyethylene bottles (Ecoflac, B. Braun Medical). The stability of undiluted tropisetron in polypropylene syringes (Plastipak, Becton-Dickinson) was also studied.

Chromatographic analysis

Assay of tropisetron was performed by high-performance liquid chromatography (HPLC) with Merck-Hitachi L5000 LC gradient controller and 655 A-11 pump, L-4250 UV/visible detector (detection wavelength 284 nm) and D2000 integrator, and a Rheodyne 7125 20-μL injection loop. Compounds were separated on a 125 mm × 4 mm LiChrospher 5 RP18 type C_{18} end-capped column (Macherey-Nagel); the mobile phase was 25 : 75

(v/v) acetonitrile (Carlo Erba)-potassium phosphate buffer, pH 7; 0·5% triethylamine (Prolabo) was added to the mobile phase. The flow rate was 1 mL min^{-1}. The internal standard used was ondansetron (Glaxo).

Standard solutions were prepared by dilution of stock solutions of tropisetron (1 mg mL^{-1}) and ondansetron (2 mg mL^{-1}) with water to give tropisetron concentrations of 5, 10, 20 and 40 $\mu g\ mL^{-1}$ and a fixed ondansetron concentration of 10 $\mu g\ mL^{-1}$. Stock solutions were stored in borosilicate-glass bottles. Before use the chromatographic method was validated specifically for study of tropisetron stability. It should enable the detection and separation of tropisetron from any breakdown products. To check this, we induced total breakdown of tropisetron by variation of pH over a wide range (with 5 M NaOH) and strong heating (boiling for 5 min). The solution obtained was then analysed by chromatography to ensure the absence of spurious effects from the breakdown products.

Stability study design

The stability of tropisetron was evaluated under different storage conditions used in clinical practice. The drug can be administered directly in a perfusion line carrying a solution. In this case it is prepared undiluted in a polypropylene syringe and its concentration is therefore as supplied, i.e., 1 mg mL^{-1}. It can also be diluted, usually with 5% glucose or saline, to a concentration of 50 $\mu g\ mL^{-1}$. We studied the stability of tropisetron after dilution with 5% glucose and saline in glass bottles, poly(vinyl chloride) bags and Ecoflac polyethylene containers. The different solutions of tropisetron prepared in bottles, bags and syringes were stored under different conditions: daylight at room temperature; dark at room temperature; and under refrigeration at +4°C. Room temperature was between 20 and 25°C. Fluorescent tube lighting was not used for our experiments—the tropisetron solutions were exposed to daylight to simulate the storage conditions observed in clinical practice. The solutions were placed in the middle of the laboratory rather than near a window in the sunlight. For polypropylene, nine syringes containing 1 mg mL^{-1} tropisetron were prepared: three were stored in daylight at room temperature, three in the dark at room temperature, and three in a refrigerator at 4°C. For each other container (glass, poly(vinyl chloride) and polyethylene), eighteen preparations of 50 $\mu g\ mL^{-1}$ tropisetron were prepared. Nine were diluted with 5% glucose and nine with saline. Of each group of nine preparations, three were kept in daylight at room temperature, three in the dark at room temperature, and three under refrigeration at 4°C. An initial sample of each solution was taken immediately after dilution and preparation, and the concentration of tropisetron obtained taken as reference (T0). Samples were then taken after 1, 2, 4 and 6 h on day 1, and then on days 2, 3, 4, 5, 8, and 15. The operating conditions for the stability study are described in Table 1.

Table 1. Study of the stability of tropisetron: experimental conditions.

Container	Solvent for dilution	Concentration of tropisetron	Storage conditions
Polypropylene syringe	No Solvent	1 mg mL^{-1}	Daylight and room temperature Dark and room temperature Under refrigeration at +4 °C
Glass bottle	5% Glucose	50 $\mu g\ mL^{-1}$	Daylight and room temperature Dark and room temperature Under refrigeration at +4 °C
	0·9% NaCl	50 $\mu g\ mL^{-1}$	Daylight and room temperature Dark and room temperature Under refrigeration at +4 °C
Poly(vinyl chloride) bag	5% Glucose	50 $\mu g\ mL^{-1}$	Daylight and room temperature Dark and room temperature Under refrigeration at +4 °C
	0·9% NaCl	50 $\mu g\ mL^{-1}$	Daylight and room temperature Dark and room temperature Under refrigeration at +4 °C
Polyethylene container	5% Glucose	50 $\mu g\ mL^{-1}$	Daylight and room temperature Dark and room temperature Under refrigeration at +4 °C
	0·9% NaCl	50 $\mu g\ mL^{-1}$	Daylight and room temperature Dark and room temperature Under refrigeration at +4 °C

Methods of calculation and statistical analysis of results

Means of the three values obtained at each sampling time were calculated, for each material, each dilution solvent, and each set of storage conditions. The mean concentrations of tropisetron were then expressed as percentages of the initial concentration at T0, taken as 100%. To evaluate the significance of any differences in stability caused by the materials, the solvents, or the storage conditions, the results were analysed statistically by analysis of variance with several factors, one of which was repeated, followed by multiple comparisons (Neumann-Keuls). The significance threshold was 0·05.

Results and Discussion

Chromatographic analysis

The tropisetron assay method was validated. The precision (repeatability and reproducibility) was satisfactory, with coefficients of variation $< 10\%$ ($n = 10$). The linearity of the method was good for concentrations from 5 to 40 $\mu g\,mL^{-1}$; the correlation coefficient, r, was 0·9997 ($r^2 = 0{\cdot}9994$).

The equation for the mean calibration plot was $y = 0{\cdot}143x + 0{\cdot}260$. The chromatographic method was validated as an analytical method for the stability study. It enabled tropisetron to be assayed specifically and independently of its degradation products. The HPLC analysis of the deliberately decomposed solution of tropisetron showed that no degradation products or other components interfered with the response of the initial drug.

Stability of tropisetron in polypropylene syringes

The results of the study are shown in Table 2. We observed no significant variation in the concentration of tropisetron with time ($P = 0{\cdot}203$). After 15 days in polypropylene syringes the concentration of tropisetron varied by no more than 10% relative to the initial concentration obtained at T0, irrespective of the storage conditions. Overall, the conditions of light and temperature did not affect the stability of 1 $mg\,mL^{-1}$ tropisetron in polypropylene syringes ($P = 0{\cdot}293$).

Stability of tropisetron in glass bottles, polyethylene containers (ecoflac) and poly(vinyl chloride) bags

The results obtained from determination of the stability of tropisetron in glass, poly(vinyl chloride) and polyethylene containers (after dilution in 5% glucose or saline) are shown in Tables 3–5. The results obtained are comparable for all the materials —storage materials led to no significant difference in tropisetron concentration ($P = 0{\cdot}764$ for glass, 0·544 for polyethylene and 0·889 for poly(vinyl chloride)). The physical and chemical stability of tropisetron were unaffected by the light and temperature conditions. The concentration of tropisetron was not changed significantly by dilution solvent (glucose or saline) ($P = 0{\cdot}936$ for glass, 0·959 for polyethylene and 0·979 for poly(vinyl chloride)). In contrast, we found a significant variation in the concentration of tropisetron with increasing time ($P < 0{\cdot}0001$ for all three materials). However, it is difficult to consider these variations as true loss of the product with time. No peaks of breakdown products of tropisetron were observed, and the concentration of tropisetron did not fall evenly with time but oscillated about the initial concentration obtained at T0. Also, these variations never exceeded 10% of the initial concentration, which is an accepted qualitative criterion of stability (Trissel 1994).

The results obtained show that undiluted tropisetron is stable in polypropylene syringes under a

Table 2. Stability of tropisetron in polypropylene syringes.

	Amount of initial concentration remaining after storage (%; mean ± s.d.)				
	1 h	2 h	4 h	6 h	1 day
Daylight* and room temperature†	103·4 ± 3·3	103·1 ± 8·5	105·4 ± 6·7	106·0 ± 8·5	107·9 ± 5·9
Dark and room temperature	95·5 ± 5·7	98·6 ± 7·6	98·5 ± 8·1	93·3 ± 7·8	101·2 ± 10·5
Under refrigeration at 4°C	97·3 ± 3·0	96·3 ± 0·9	100·2 ± 2·1	98·7 ± 3·3	97·8 ± 1·2
	2 days	3 days	4 days	8 days	15 days
Daylight* and room temperature†	104·0 ± 5·3	104·8 ± 9·8	101·1 ± 7·1	103·1 ± 6·1	102·4 ± 7·8
Dark and room temperature	99·5 ± 4·4	96·3 ± 4·5	96·8 ± 6·2	99·1 ± 8·2	97·5 ± 5·2
Under refrigeration at 4°C	98·5 ± 1·8	96·5 ± 2·6	95·7 ± 3·7	98·0 ± 3·3	96·9 ± 1·4

* Light conditions observed in clinical practice. †20–25 °C.

Table 3. Stability of tropisetron in glass bottles after dilution with 5% glucose or with 0.9% NaCl.

	Amount of initial concentration remaining after storage (%; mean ± s.d.)				
	1 h	2 h	4 h	6 h	1 day
5% Glucose					
Daylight* and room temperature†	97·9 ± 6·2	90·0 ± 10·3	90·1 ± 8·8	92·7 ± 2·7	101·0 ± 2·9
Dark and room temperature	108·4 ± 8·2	90·9 ± 7·2	91·2 ± 5·1	93·6 ± 10·8	110·0 ± 1·9
Under refrigeration at 4°C	101·0 ± 8·0	92·6 ± 5·0	95·4 ± 5·2	97·5 ± 8·3	110·0 ± 9·9
0·9% Sodium Chloride					
Daylight* and room temperature†	103·2 ± 1·6	101·5 ± 4·0	101·3 ± 3·1	97·5 ± 1·1	105·2 ± 2·5
Dark and room temperature	99·4 ± 5·3	96·4 ± 1·8	95·6 ± 3·1	95·8 ± 1·8	103·1 ± 2·6
Under refrigeration at 4°C	100·5 ± 2·3	99·0 ± 1·4	96·7 ± 2·9	98·2 ± 5·9	102·2 ± 0·6
	2 days	3 days	4 days	8 days	15 days
5% Glucose					
Daylight* and room temperature†	97·9 ± 4·0	99·1 ± 5·5	107·6 ± 2·5	101·7 ± 3·2	97·6 ± 3·0
Dark and room temperature	105·4 ± 3·5	105·2 ± 1·2	110·0 ± 4·4	103·8 ± 1·9	103·7 ± 1·1
Under refrigeration at 4°C	107·7 ± 7·6	106·9 ± 7·6	109·1 ± 9·0	106·7 ± 8·6	103·0 ± 11·1
0·9% Sodium Chloride					
Daylight* and room temperature†	97·4 ± 4·6	102·7 ± 2·4	102·8 ± 0·7	109·9 ± 5·1	104·8 ± 2·8
Dark and room temperature	95·1 ± 4·7	100·6 ± 0·4	99·6 ± 2·7	109·7 ± 3·1	103·9 ± 2·9
Under refrigeration at 4°C	94.8 ± 3·3	98·6 ± 2·4	99·8 ± 2·1	109·2 ± 1·6	101·9 ± 2·5

* Light conditions observed in clinical practice. † 20–25 °C.

Table 4. Stability of tropisetron in poly(vinyl chloride) bags after dilution with 5% glucose or with 0·9% NaCl.

	Amount of initial concentration remaining after storage (%; mean ± s.d.)				
	1 h	2 h	4 h	6 h	1 day
5% Glucose					
Daylight* and room temperature†	99·2 ± 1·8	101·7 ± 1·9	103·2 ± 6·9	102·2 ± 4·2	103·6 ± 4·1
Dark and room temperature	99·9 ± 2·6	102·6 ± 4·2	102·7 ± 5·1	102·1 ± 4·4	103·1 ± 6·7
Under refrigeration at 4°C	99·4 ± 5·4	101·3 ± 8·7	100·3 ± 6·4	96·8 ± 6·0	96·6 ± 6·8
0·9% Sodium Chloride					
Daylight* and room temperature†	99·5 ± 2·6	96·7 ± 2·0	96·4 ± 2·2	97·4 ± 1·2	100·0 ± 5·0
Dark and room temperature	99·1 ± 1·1	101·4 ± 2·6	99·9 ± 1·8	98·8 ± 3·1	104·1 ± 2·7
Under refrigeration at 4°C	103·0 ± 7·4	98·9 ± 5·3	99·3 ± 7·7	98·3 ± 6·5	102·2 ± 11·1
	2 days	3 days	4 days	8 days	15 days
5% Glucose					
Daylight* and room temperature†	101·0 ± 3·7	103·6 ± 3·1	97·4 ± 2·3	100·4 ± 0·9	104·2 ± 3·1
Dark and room temperature	99·2 ± 1·9	97·3 ± 4·7	95·0 ± 3·5	97·5 ± 5·0	107·1 ± 3·4
Under refrigeration at 4°C	98·7 ± 8·8	95·2 ± 7·4	95·4 ± 7·1	95·7 ± 4·8	108·2 ± 4·5
0·9% Sodium Chloride					
Daylight* and room temperature†	99·6 ± 5·5	94·6 ± 3·6	97·4 ± 4·6	99·6 ± 3·8	99·2 ± 8·5
Dark and room temperature	103·8 ± 0·9	98·0 ± 1·7	99·1 ± 2·3	106·9 ± 4·4	103·8 ± 1·5
Under refrigeration at 4°C	102·2 ± 11·0	96·4 ± 6·8	101·3 ± 6·5	106·5 ± 8·7	105·6 ± 9·0

* Light conditions observed in clinical practice. † 20–25 °C.

Table 5. Stability of tropisetron in polyethylene containers after dilution with 5% glucose or with 0·9% NaCl.

	Amount of initial concentration remaining after storage (%; mean ± s.d.)				
	1 h	2 h	4 h	6 h	1 day
5% Glucose					
Daylight* and room temperature†	97·2 ± 3·4	97·5 ± 1·6	97·9 ± 3·0	94·7 ± 2·4	98·2 ± 5·1
Dark and room temperature	99·1 ± 4·4	102·9 ± 2·7	100·3 ± 2·9	96·0 ± 2·0	103·3 ± 6·7
Under refrigeration at 4°C	97·9 ± 1·9	98·6 ± 3·7	100·6 ± 6·1	92·5 ± 3·7	101·1 ± 3·0
0·9% Sodium Chloride					
Daylight* and room temperature†	97·7 ± 8·4	97·0 ± 8·0	97·4 ± 6·8	96·4 ± 7·6	101·7 ± 9·2
Dark and room temperature	99·4 ± 2·0	94·9 ± 6·5	96·0 ± 2·6	94·7 ± 6·1	94·1 ± 7·8
Under refrigeration at 4°C	99·0 ± 2·5	100·5 ± 0·7	100·9 ± 1·8	104·4 ± 4·8	102·3 ± 1·9
	2 days	3 days	4 days	8 days	5 days
5% Glucose					
Daylight* and room temperature†	100·0 ± 3·7	100·5 ± 7·5	100·6 ± 2·4	94·9 ± 3·6	100·1 ± 4·8
Dark and room temperature	99·7 ± 0·9	94·6 ± 5·5	98·4 ± 4·5	97·3 ± 4·8	99·5 ± 2·8
Under refrigeration at 4°C	98·2 ± 9·0	95·2 ± 2·4	98·1 ± 3·1	93·0 ± 3·2	97·1 ± 4·8
0·9% Sodium Chloride					
Daylight* and room temperature†	105·2 ± 6·4	93·0 ± 4·5	96·4 ± 3·5	95·0 ± 8·8	95·5 ± 4·3
Dark and room temperature	102·0 ± 7·0	93·3 ± 8·1	92·0 ± 5·0	95·0 ± 5·7	93·5 ± 3·3
Under refrigeration at 4°C	105·8 ± 6·1	100·9 ± 1·6	99·4 ± 3·4	101·4 ± 3·3	102·7 ± 2·1

* Light conditions observed in clinical practice. † 20–25 °C.

range of common storage conditions. Dilution with 5% glucose or saline causes wider variations in tropisetron concentration with time (no more than 10% of initial concentrations, however). Hence it is preferable to store tropisetron undiluted as supplied (1 mg mL^{-1}) and make up dilutions in 5% glucose or saline extemporaneously. After dilution, tropisetron can be administered equally well in glass bottles, poly(vinyl chloride) bags, or Ecoflac polyethylene containers; all these materials are highly compatible with the drug.

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