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Journal of Chromatography A, 690 (1995) 71–76

JOURNAL OF CHROMATOGRAPHY A

Stability study and content uniformity of prochlorperazine in pharmaceutical preparations by liquid chromatography

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First received 22 March 1994; revised manuscript received 5 August 1994

Abstract

The stability of prochlorperazine (PCZ) in pharmaceutical admixtures and the content uniformity of its dosage forms were examined by liquid chromatography. The drug and internal standard (imipramine) were separated on a CN Radial-Pak cartridge using sodium acetate solution (0.018 *M*)–acetonitrile (5:95, v/v) as the mobile phase, and were detected in the eluate at 250 nm. The assay was highly linear ($r > 0.993$), and the relative standard deviations (R.S.D.s) at 5, 12.5 and 25 μg/ml were 7.8, 4.1, and 4.3%, respectively. The deviations from perfect accuracy at these concentrations were 6.4, 1.6, and 6.0%, respectively. The mean percentages (with R.S.D.s) of the labelled claim found in a commercially available injection, syrup, tablet and suppository were 103.9 (3.5%), 103.8 (3.6%), 100.5 (1.5%) and 101.1 (5.0%), respectively. Although the drug was stable in sterile dextrose solution (5%, w/v) at 4°C (refrigeration) with protection from light, it degraded rapidly in a bi-exponential fashion at 23°C (room temperature), particularly when unprotected from light. Poorer stability was observed under all conditions examined when PCZ was formulated in normal saline.

1. Introduction

Prochlorperazine, 2-chloro-10-[3-(1-methylpiperazinyl)propyl]phenothiazine (PCZ), is an antiemetic and antipsychotic agent widely used in the prevention and control of nausea and vomiting [1,2] associated with chemotherapy or radiation treatment of cancer. The drug is often dispensed by the hospital pharmacy to the patient's bedside in the form of an intravenous admixture; however, for clinical reasons or after death it may remain unused, requiring disposal. This may prove to be expensive and troublesome if it occurs frequently, particularly in major cancer centres. Unfortunately, no data are available on the stability of PCZ to evaluate the feasibility of preserving these preparations for use in different patients.

Although a few liquid chromatographic (LC) methods have been reported for the determination of PCZ [3–6], LC has not been used to examine the stability of the drug in pharmaceutical admixtures. Unlike in spectrophotometry, in LC the compounds are separated prior to determination.

This study was undertaken to examine the

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0021-9673/95/$09.50
SSDI 0021-9673(94)00897-3

stability of prochlorperazine in intravenous admixtures under different storage conditions and to investigate the content uniformity of its commercially available dosage forms by use of an LC method.

2. Experimental

2.1. Materials

Analytical samples of prochlorperazine edisylate and imipramine hydrochloride (internal standard) were supplied by Sigma (St. Louis, MO, USA). Acetonitrile, pentane, 2-propanol (all from Fisher, Fair Lawn, NJ, USA) and sodium acetate (Fluka, Buchs, Switzerland) were of HPLC grade. Water for HPLC was generated by passing "reverse osmosis" water through a 0.45-μm membrane filter (Millipore, Milford, MA, USA).

2.2. Pharmaceutical formulations

Four commercially available formulations of prochlorperazine, i.e., 10-mg tablets, 5-mg suppositories, 5 mg per 5 ml syrup (Compazine; Smith Kline and French, Philadelphia, PA, USA) and 5 mg/ml injections (Prochlorperazine Edisylate USP; Wyeth, Philadelphia, PA, USA), obtained from a local hospital pharmacy were analysed for their content uniformity of PCZ.

2.3. Instrument

The chromatograph (Waters, Milford, MA, USA) consisted of a system controller (Model 720), a solvent-delivery pump (Model 6000A), an autosampler (Model 710B WISP), a radial compression module (RCM 8×10) equipped with a μBondpack CN Radial-Pak cartridge and a Guard-Pak precolumn module with a CN insert, a variable-wavelength UV–visible detector (Lambda-Max Model 480) set at 250 nm and a data module (Model 730). The mobile phase was a mixture of sodium acetate solution (0.018 *M*) and acetonitrile (5:95, v/v), filtered and degassed before use. The flow-rate was 4 ml/min at a pressure of <1000 lb/in.^{2}.

2.4. Calibration

The concentration of PCZ in the test samples was calculated by use of calibration graphs (peak-height ratio versus concentration) in the range 5–25 μg/ml of PCZ on different days. The linearity of the assay was also established by constructing calibration graphs in the range 2–50 μg/ml. To 200-μl aliquots of a freshly prepared stock standard solution of the internal standard in water (100 μg/ml), different volumes of a freshly prepared stock standard solution of PCZ in water (1 mg/ml) were added and the final volume of each sample was brought to 2 ml with water to yield concentrations in the above range. The solutions were transferred to microvials and the autosampler was programmed to inject 200 μl of each solution.

2.5. Precision

The intra-run (within-day) precision was investigated by analysing replicate samples of PCZ in aqueous solutions at concentrations of 5, 12.5 and 25 μg/ml. The preparation of the samples and the analysis were performed as described above.

2.6. Stability study

The stability of PCZ in sterile normal saline (NS) and dextrose (5%, w/v) (DX) solutions was investigated under three different conditions: room temperature (i.e., 23°C) with protection from light (RT-LP), room temperature with no protection from light (RT-LUP) and at 4°C (refrigeration) with protection from light (RF-LP). On the day of the experiment, an appropriate volume of an injection of PCZ (5 mg/ml) was thoroughly mixed with sterile NS or DX solution to yield a concentration of PCZ equivalent to 20 mg/l. A 200-μl volume of this solution stored under RT-LP, RT-LUP or RF-LP conditions was diluted to 2 ml with water and placed in an autosampler vial, and the autosampler

(which was protected from light with aluminium foil for the LP experiment) was programmed to inject 200 μl every 15 min for 13 h. To maintain the RF-LP condition, a 200-μl autosampler microvial placed in an autosampler vial filled with ice was used, and the diluted solution, which was kept at 4°C, was replenished between injections. The concentration of PCZ was calculated using calibration graphs constructed daily from fresh stock standard solutions prepared immediately prior to each experiment.

2.7. Determination of prochlorperazine in dosage forms

Tablets

The tablet was pulverized into a fine powder and carefully placed in a 1-l volumetric flask. After dilution to volume with water, the liquid was thoroughly mixed and stirred for 2 h using a magnetic stirrer and filtered. Triplicate samples (9 ml each) of the filtrate were taken quickly and analysed as described above after the addition of the internal standard (1 ml of 100 μl/ml solution). The concentration of PCZ was calculated using a calibration graph prepared under similar conditions. Ten different tablets were analysed.

Injections

A 2-ml aliquot of the injection solution (5 mg/ml) was carefully placed in a 1-l volumetric flask and diluted to volume with water. After the liquid has been thoroughly mixed, triplicate samples (9 ml each) of the solution were taken and analysed as described above after the addition of internal standard (1 ml of 100 μg/ml solution). Ten different injection units were analysed.

Syrup

A 1-ml volume of syrup (5 mg per 5 ml) was placed in a 100-ml volumetric flask and diluted to volume with water. After the liquid had been thoroughly mixed, triplicate samples (9 ml each) of the solution were taken and analysed as described above after the addition of internal standard (1 ml of 100 μg/ml solution). Five different batches of syrup were analysed.

Suppositories

A suppository was carefully unwrapped and weighed, and one fifth of the total mass (equivalent to 1 mg of PCZ) was cut out and placed in a 100-ml volumetric flask containing 80 ml of 2-propanol–pentane (3:97, v/v). After the flask had been tightly sealed, the liquid was thoroughly shaken then stirred for 15 min. After dilution to volume with the above organic solvent mixture and thorough mixing, the extract was filtered. Duplicate samples of the filtrate were dried under a stream of nitrogen after addition of the internal standard, and the residue was reconstituted with 200 μl of the mobile phase and analysed as described above. Complete recovery (>97%) was obtained with this extraction procedure. Ten different suppositories were analysed.

3. Results and discussion

Fig. 1 shows a typical chromatogram for PCZ in a diluted tablet extract sample supplemented with an appropriate amount of the internal standard (I.S.). Under the described conditions the compounds were fully resolved and yielded sharp and symmetrical peaks with a total chromatographic time of less than 7.5 min.

The concentration of PCZ in the pharmaceutical preparations examined was calculated by use of peak-height ratio (PCZ/I.S.) (*PHR*) versus concentration (*C*) calibration graphs constructed immediately prior to analysis under similar conditions. The assay was highly linear ($PHR = 0.0068 \pm 0.00066 + 0.1147 \pm 0.0072C$) with correlation coefficients (r) ranging between 0.993 and 0.999. The intercept and slope of this equation represent the mean ± S.D. of ten determinations. The intra-run precision was equally good with relative standard deviations (R.S.D.s) at 5, 12.5 and 25 μg/ml of 7.8, 4.1 and 4.3% (Table 1); the deviations from perfect accuracy at these concentrations were 6.4, 1.6, and 6.0%, respectively (Table 1).

The content uniformity of four different commercially available dosage forms of PCZ were examined according to the described procedure,

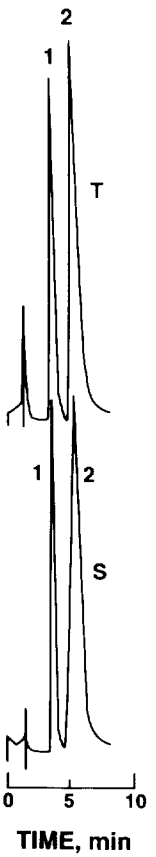

Fig. 1. Representative chromatograms of a tablet extract (T) and a standard sample (S) of PCZ (peak 2). Each of these samples contained 10 μg/ml of the internal standard (peak 1), and the concentrations of PCZ were 13.6 μg/ml (measured) and 12.5 μg/ml, respectively.

and the results obtained are presented in Table 2. The mean percentages (with R.S.D.s) of the labelled claim found in ten injections, five

Table 2
Content uniformity of commercial prochlorperazine formulations

Unit no.	Percentage of labelled claim			
	Tablet	Suppository	Injection	Syrup
1	99.3	106.5	102.2	105.3
2	99.5	96.6	106.8	104.1
3	100.1	93.4	108.7	97.6
4	99.0	105.6	103.8	104.3
5	100.0	99.5	101.0	107.6
6	98.6	102.4	105.8	
7	102.3	102.0	101.2	
8	102.5	98.0	96.9	
9	102.5	97.7	104.6	
10	101.3	109.5	107.7	
Mean	100.5	101.1	103.9	103.8
R.S.D. (%)	1.5	5.0	3.5	3.6

syrups, ten tablets and ten suppositories were 103.9 (3.5%), 103.8 (3.6%), 100.5 (1.5%) and 101.1 (5.0%), respectively, which fall within the content uniformity limits specified by the USP (Table 2).

The stability of PCZ in sterile normal saline (NS) and dextrose (5%, w/v) (DX) solutions at a concentration equivalent to 20 mg/l was examined under RM-LP, RM-LUP and RF-LP conditions as described above. Although the drug was stable in DX solution when kept in a refrigerator (RF-LP), it degraded rapidly at room temperature in a bi-exponential fashion (Fig. 2):

$$C = Q\,e^{-\alpha t} + R\,e^{-\delta t} \quad (1)$$

where C is the concentration of the drug remain-

Table 1
Accuracy and precision of the method

Concentration prepared (μg/ml)	Concentration found[a] (μg/ml)	R.S.D. of concentration[a] (%)	Deviation from perfect accuracy[b] (%)
5.0	4.68	7.8	6.4
12.5	12.70	4.3	1.6
25.0	26.50	4.1	6.0

[a] $n = 10$.
[b] Estimated as 100(concentration prepared − concentration found)/concentration prepared.

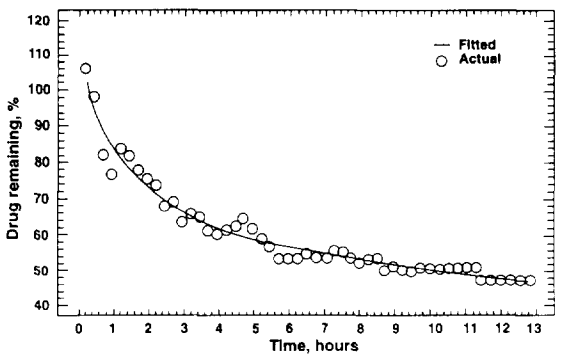

Fig. 2. Stability profile of PCZ (20 mg/l) in sterile dextrose solution (5%, w/v) stored at room temperature (23°C) unprotected from light (DX, RT-LUP). The data were fitted to a bi-exponential equation and the solid line represents the best fit.

ing, σ and Q are the apparent first-order rate constant and pre-exponential coefficient for the rapid phase of degradation (or disappearance) of the drug, respectively, and δ and R are the apparent first-order rate constant and pre-exponential coefficient for the slow phase of degradation, respectively. Hence it appears that the drug undergoes a reversible reaction ($A \rightleftharpoons B$), and its chemical decomposition occurs irreversibly (to an unspecified specie) only when it is in the original form (A), or

$$\begin{array}{c} A \rightleftharpoons B \\ \downarrow \end{array}$$

The percentage of the drug remaining was fitted non-linearly to Eq. 1 using the STATGRAPHICS Statistical Graphic System package (Statistical Graphics, Rockville, MD, USA), and the rapid (σ) and slow (δ) rate constants of degradation of PCZ in solution were generated (Table 3). The corresponding half-lives ($t_{1/2\sigma}$ and $t_{1/2\delta}$, respectively) ranged between 0.082 h (NS, RT-LUP) and 1.31 h (DX, RT-LP) for the rapid phase of degradation and between 24.6 h (DX, RT-LUP) and 71.7 h (NS, RT-LP) for the slow phase of degradation. These half-lives were readily calculated from the relationship $t_{1/2\sigma} = 0.693/\sigma$ or $t_{1/2\delta} = 0.693/\delta$. As shown in Table 3, the drug in both DX and NS solutions was as expected more stable under LP than under LUP conditions. It is noteworthy that whereas the drug was stable in DX solution under refrigeration, it lost about 21% of its original amount in NS within 1.75 h, after which it remained constant for the duration of the experiment. It appears that the drug under the same temperature or light-protection conditions was more stable in the dextrose solution than in normal saline, possibly owing to the primary and secondary salt effect of sodium chloride on the velocity of the degradative reaction. Hence it may be recommended that the intravenous admixture of PCZ should be used immediately after preparation, and if there is any delay in administration, it may be utilized in patients only if formulated in dextrose solution and stored in a refrigerator away from light.

Table 3
Apparent rate constants for degradation of prochlorperazine

Storage conditions	Degradation rate constant (h^{-1})		r^2
	σ	δ	
DX, RT-LUP	0.709	0.0282	0.963
DX, RT-LP	0.527	0.0190	0.948
NS, RT-LUP	8.503	0.0265	0.940
NS, RT-LP	0.574	0.00967	0.933

NS = Normal saline; DX = dextrose (5%, w/v) sterile solutions; LP = protection from light; LUP = no protection from light; RT = room temperature (23°C); σ and δ = apparent first-order rate constants for rapid and slow phases of degradation of PCZ, respectively; r = correlation coefficient.

Acknowledgement

The authors thank the Administration of the King Faisal Specialist Hospital and Research Centre for its support of the drug analysis research programme in this institution.

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