Stability of Clozapine Stored in Oral Suspension Vehicles at Room Temperature

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ABSTRACT

Rationale: For patients who cannot or will not take medications in tablet form, a liquid formulation of clozapine is required; however, no commercial oral liquid or suspension exists.

Objective: To evaluate the stability of a 20 mg/mL clozapine suspension in 6 different suspending vehicles: Ora-Sweet, Ora-Plus, a 1:1 mixture of Ora-Sweet and Ora-Plus, the suspending vehicle used by the Hospital for Sick Children, simple syrup, and a noncommercial vehicle known as Guy's pediatric mixture.

Methods: A reverse-phase, stability-indicating liquid chromatographic method with ultraviolet detection at 230 nm was validated before the study. Validation demonstrated that clozapine could be quantified accurately and reproducibly. On study day 0, 100 mL of a 20 mg/mL clozapine suspension was prepared in each of the 6 suspending vehicles. Each suspension was separated into 3 equal aliquots, which were stored in 60-mL amber plastic containers. All suspensions were stored at room temperature (23°C) without protection from light. On study days 0, 3, 6, 14, 28, and 63, the concentration of clozapine was determined by liquid chromatography, and physical inspection was performed.

Results: During the study period, all study samples retained more than 95.0% of their initial concentration. Inspection of chromatograms obtained during the stability study failed to reveal any of the degradation products that had been generated during the assay validation.

Conclusion: Suspensions of clozapine (20 mg/mL) prepared in the 6 suspending vehicles used in this study and stored in amber plastic containers at 23°C retained more than 95% of their initial concentration during 63 days of storage, regardless of the suspending vehicle.

Key words: drug stability, clozapine, suspensions, commercial suspending agents

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RÉSUMÉ

Historique : Pour les patients qui ne peuvent ou ne veulent pas prendre de médicaments sous forme de comprimés, une forme liquide de clozapine est donc nécessaire; cependant, aucune forme de clozapine liquide ou en suspension n'est offerte dans le commerce.

Objectif : Évaluer la stabilité d'une suspension de clozapine à 20 mg/mL dans six différents excipients pour suspension : Ora-Sweet, Ora-Plus, un mélange 1:1 d'Ora-Sweet et d'Ora-Plus, l'agent de suspension utilisé par le Hospital for Sick Children, un excipient non commercial connu sous le nom de mélange pédiatrique de Guy, et le sirop simple.

Méthodes : Une épreuve par chromatographie liquide en phase inverse, indicative de la stabilité, avec détection ultraviolette à 232 nm a été validée avant l'étude. La validation a montré que la clozapine pouvait être quantifiée de façon précise et reproductible. Au jour 0 de l'étude, on a préparé 100 mL d'une suspension de clozapine à 20 mg/mL dans chacun des six excipients pour suspension. Chaque préparation de suspension a été séparée en trois aliquots égaux, qui ont été entreposés dans des contenants de plastique de couleur ambre de 60 mL. Toutes les préparations de suspension ont été entreposées à la température ambiante (23 °C), non protégées de la lumière. Aux jours 0, 3, 6, 14, 28 et 63 de l'étude, la concentration de clozapine a été déterminée par chromatographie liquide et une inspection physique a été effectuée.

Résultats : Au cours de la période de l'étude, tous les échantillons ont conservé plus de 95,0 % de leur concentration initiale. L'inspection des chromatogrammes obtenus par l'épreuve de stabilité n'a pu révéler aucun des produits de dégradation générés durant la validation du procédé d'analyse.

Conclusion : Les suspensions de clozapine (20 mg/mL) préparées dans les six excipients pour suspension utilisés dans cette étude, puis entreposés dans des contenants de plastique ambrés à 23 °C ont conservé plus de 95 % de leur concentration initiale pendant 63 jours d'entreposage, indépendamment de l'excipient pour suspension utilisé.

Mots clés: stabilité médicamenteuse, clozapine, suspensions, agents de suspension commerciaux

INTRODUCTION

Clozapine is indicated for the management of symptoms in treatment-resistant schizophrenia. This drug is available as 25-mg and 100-mg uncoated tablets.[1] A liquid formulation is required for patients who cannot or will not take tablets, but no commercial oral liquid exists. The stability of a 20 mg/mL clozapine suspension prepared by suspending crushed tablets in an oral solution referred to as Guy's pediatric mixture has been described.[2] Guy's pediatric mixture contains sucrose, carboxymethylcellulose, methyl hydroxybenzoate, and propylhydroxybenzoate and is not commercially available. The clozapine suspension prepared with this vehicle demonstrated no change in concentration when stored for 18 days at room temperature. However, preparation of Guy's pediatric mixture is time-consuming and tedious. Various other vehicles are available, including some products that may be purchased commercially, but the stability of clozapine in these vehicles is unknown.

The objective of this study was to evaluate the stability of a 20 mg/mL clozapine suspension in 6 different suspending vehicles — Ora-Sweet, Ora-Plus, a 1:1 mixture of Ora-Sweet and Ora-Plus, the suspending vehicle used by the Hospital for Sick Children, simple syrup, and Guy's pediatric mixture — when stored for 9 weeks at room temperature.

METHODS

Chromatographic Analysis

The liquid chromatographic system consisted of a solvent delivery pump (model P4000, Thermo Separation Products, San Jose, California), which pumped a mixture of 31.5% acetonitrile (EM Science, distributed by BDH, Toronto, Ontario, catalogue no. AX0142-1) and 68.5% 0.05 mol/L potassium phosphate monobasic at pH 4.1 (Fisher Scientific, Toronto, Ontario, catalogue no. P286) through a 15 cm x 4.6 mm reverse-phase C_{18}, 3-µm column (Supelcosil ABZ plus, Supelco, Oakville, Ontario) at 1.0 mL/min. Samples were injected directly onto the liquid chromatography column, in duplicate, using an autoinjector (Ultra WISP 715, Waters Limited, Toronto, Ontario). The column effluent was monitored with a variable-wavelength ultraviolet detector (UV 6000, Thermo Separation Products) at 230 nm. Signals from the detector were integrated and recorded with a PC1000 chromatography data system (Thermo Separation Products). The area under the clozapine peak at 230 nm was subjected to least-squares linear regression, and the actual clozapine concentration in each sample was determined by interpolation from the standard curve. These concentrations were then converted to a concentration in milligrams per millilitre by use of the dilution factor (100). The quantitative resolution (standard deviation of duplicates/slope) for standards observed during assay validation was never greater than 0.0035 mg/mL. On the basis of the quantitative resolution, clozapine concentrations were recorded to the nearest 0.001 mg/mL but were reported to the nearest 0.01 mg/mL.

Assay Validation

Following development of the chromatographic system for clozapine, the suitability of this method for use as a stability-indicating assay was tested by analyzing samples of clozapine that had been subjected to accelerated degradation with sodium hypochlorite. Clozapine 12.5 mg (Sigma-Aldrich Canada Limited, Oakville, Ontario, lot 10K1204) was dissolved in 25 mL of methanol to make a 0.5 mg/mL stock solution. One millilitre of this stock solution was placed in a 5-mL glass test tube. Various volumes (between 5 µL and 100 µL) of sodium hypochlorite solution (1% available chlorine; Hygeol, Wampole Canada Inc, Scarborough, Ontario, lot 8A037A) were added to this solution. The mixture was combined with a vortex mixer (Fisher Vortex Genie 2, Fisher Scientific) and chromatography was performed immediately. Chromatograms were inspected for the appearance of additional peaks, and the clozapine peak was compared between samples for changes in concentration, retention time, and shape.

After this first phase of evaluation and validation, the accuracy (the percentage deviation from the known concentration) and reproducibility (the coefficient of variation, determined as standard deviation/mean, expressed as a percentage) of the standard curves and quality control samples were tested over 4 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance on each study day.

Stability Study

On study day 0, 100 mL of a 20 mg/mL clozapine suspension was prepared in each of 6 different suspending vehicles. The suspending vehicles were Ora-Sweet (Wiler PCCA, London, Ontario), Ora-Plus (Wiler PCCA), a 1:1 mixture of Ora-Sweet and Ora-Plus (purchased separately and mixed), the suspending vehicle used by the Hospital for Sick Children (methylcellulose 1500 CPS; Wiler PCCA), simple syrup (Wiler PCCA), and Guy's pediatric mixture. Each suspension was separated into 3 equal aliquots and stored in 60-mL low-density polyethylene amber containers (Jones Packaging Inc, London, Ontario). All 18 containers (3 containers each of the 6 suspensions) were stored at room temperature (23°C) without protection from ambient fluorescent room light, to simulate the storage conditions encountered in routine hospital pharmacy practice.

Physical Inspection

On study days 0, 3, 6, 14, 28, and 63, samples drawn from each of the 18 sample containers for the purpose of liquid chromatography were inspected visually for caking and consistency as well as for changes in colour.

Clozapine Analysis

On each study day (days 0, 3, 6, 14, 28, and 63), standard curves were prepared by dissolving 10.0 mg of clozapine (Sigma-Aldrich Co, lot 10K1204) in 25 mL of methanol to make a 0.4 mg/mL stock solution. Samples of this stock solution were further diluted with distilled water to obtain standards with final concentrations of 0.3, 0.2, 0.15, 0.10, 0.075, and 0.050 mg/mL. These standards, along with a blank, were used to construct a standard curve. One-microlitre samples of each standard or blank were chromatographed in duplicate. In addition, 2 quality control samples of clozapine (concentrations 0.075 and 0.30 mg/mL) were chromatographed in duplicate each day; the concentrations of the quality control samples were determined and compared with the known concentrations. Intra-day and inter-day errors were assessed by the coefficients of variation of the peak areas of both quality control samples and standards.

On each study day, suspension samples drawn from each container were assayed for clozapine content. All samples initially had a nominal clozapine concentration of 20 mg/mL. Samples were prepared for assay by dissolving 1.0 mL of each suspension in 100 mL of methanol to prepare a solution with nominal concentration of 0.20 mg/mL. This solution was mixed with a vortex mixer and sonicated until no particulate matter was evident. One microlitre of each diluted sample solution was injected directly onto the liquid chromatography system without further preparation. All samples were analyzed in duplicate. The concentration of clozapine in each of the replicates was determined by interpolation from a standard curve of 6 standards plus a blank. These concentrations were then multiplied by the dilution factor (100) to determine the clozapine concentration in milligrams per millilitre, recorded to the nearest 0.001 mg/mL.

Data Reduction and Statistical Analysis

After the coefficient of variation of the assay had been determined, a power calculation indicated that duplicate injection had the ability to distinguish between concentrations that differed by at least 10%.[3,4] Means were calculated for replicated analyses and are reported in Table 1. Mean results from different days for each container were compared statistically (by linear regression) to determine if there was an association between the observed result and time. The lower limit of the regression line, based on a 95% confidence interval (CI), was also determined. Clozapine concentrations were considered acceptable or within acceptable limits if the concentration on any day of analysis was greater than 90% of the initial concentration (on day 0) and the lower limit of the 95% CI exceeded 90% remaining. Analysis of variance was used to test differences in degradation rate between different vehicles. Multiple linear regression was also used to detect any effect of time and suspension vehicle on concentration during the study period (by means of SPSS for Windows, release 10.0.5, 1999). The 5% level was used as the a priori cut-off for significance.

RESULTS

Accelerated Degradation and Assay Validation

At room temperature, a 0.5 mg/mL solution of clozapine in water to which 100 µL of 1% sodium hypochlorite had been added degraded rapidly, such that only 7.9% of the original concentration remained after 5 min. In samples to which smaller amounts of sodium hypochlorite were added, a greater percentage of the initial concentration remained after 5 min. In the degraded samples, several potential degradation products eluted before 4 min and at 6.4 min. None of the degradation products interfered with clozapine quantification (Figure 1). At room temperature, a

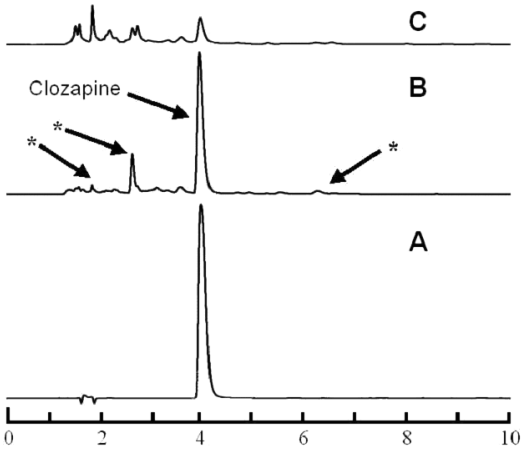

Figure 1. Representative chromatograms of clozapine in methanol (panel A) and during the accelerated degradation study (panel B). For the degradation study, 25 µL of 1% sodium hypochlorite was added to 1 mL of a 0.5 mg/mL clozapine solution (panel B); the sample for analysis was obtained when 50% of the initial clozapine remained. Several potential degradation products eluted before 4 min and at 6.4 min; each of the largest peaks is marked with an arrow and an asterisk. A third chromatogram (panel C) shows degradation of clozapine when 75 µL of 1% sodium hypochlorite was added to 1 mL of a 0.5 mg/mL clozapine solution. None of the degradation products interfered with clozapine quantification, and none were positively identified.

Table 1. Observed Concentration (as Mean Percent of Initial Concentration) of Clozapine after Storage in Various Suspending Vehicles

Study Day	Ora-Sweet	Ora-Plus	1:1 Mixture Ora-Sweet and Ora-Plus	HSC Suspending Vehicle	Simple Syrup	Guy's Pediatric Mixture
Initial concentration (mg/mL)*	19.98 ± 0.17	19.86 ± 0.18	19.84 ± 0.30	18.43 ± 0.06†	19.37 ± 0.19	20.14 ± 0.06
Day 3	100.21 ± 1.52	100.09 ± 2.95	102.38 ± 2.56	101.96 ± 1.38	103.95 ± 0.67	99.94 ± 0.67
Day 6	99.09 ± 1.54	97.44 ± 6.19	99.98 ± 1.72	98.40 ± 4.49	99.80 ± 1.31	102.68 ± 2.03
Day 14	96.16 ± 1.72	99.22 ± 2.39	100.65 ± 1.90	95.86 ± 1.57	95.80 ± 1.24	103.68 ± 1.20
Day 28	97.89 ± 2.12	100.65 ± 0.79	101.30 ± 1.82	101.68 ± 5.16	101.91 ± 1.08	96.71 ± 0.82
Day 63	96.97 ± 1.85	96.01 ± 0.70	100.78 ± 0.63	103.91 ± 0.64	103.92 ± 0.35	100.08 ± 2.03
Coefficient of variation (%)*	1.68	1.82	0.89	2.86	3.05	2.42
% remaining on day 63 (estimated by regression)‡	97.22	97.01	100.11	104.40	103.34	98.26
Lower limit of 95% CI for % remaining on day 63§	93.98	93.97	99.13	98.71	97.65	94.64

CI = confidence interval, HSC = The Hospital for Sick Children.
*The variability of the percent remaining over the 63-day study period is expressed as the coefficient of variation (standard deviation/mean) and is presented as a percentage, except for the initial concentration, for which variability is expressed by standard deviation. For each suspending vehicle there were 3 individual containers. On each study day, each container was sampled, and the analysis of the sample from each container was performed in duplicate. Each analysis reported the observed concentration in milligrams per millilitre. The amount remaining is based on the average concentration observed in each of the 6 replicates from each study day relative to the average concentration observed on study day 0, reported as a percentage.
†One batch of clozapine suspension had an initial concentration of 18.43 mg/mL. The initial clozapine concentration in all other containers was within 3.2% of the nominal value.
‡Percent remaining on day 63, based on linear regression. Concentrations at time zero (initial concentration) and at 63 days were determined by linear regression. Calculation: (concentration on day 63) x 100/(initial concentration).
§The 95% CI based on percentage remaining was calculated using the lower limit of the 95% CI of the slope as calculated by linear regression: {100 x [initial concentration + (slope x 63 days)]/(initial concentration)}.

0.5 mg/mL solution of clozapine in water to which no sodium hypochlorite was added did not degrade, and no degradation products were observed after 24 h of storage. Given the degradation of clozapine in the presence of sodium hydrochloride and the chromatographic separation of the degradation products from clozapine, it was concluded that this analytical method was suitable for indicating stability.[5-7]

Analysis of standard curves and quality control samples during validation indicated that the clozapine concentration was measured accurately. Mean results for duplicate determinations of standards and quality control samples over the validation period indicated deviation of less than 3% from the expected concentration. Inter-day variation in the slope (as measured by CV) averaged 5.1%. Intra-day analytical reproducibility (as measured by CV) averaged less than 1% for each of the standards and quality control samples, indicating that differences of 10% or more could be confidently detected with acceptable error rates on duplicate analysis.[3,4] During the study period, intra-day CV averaged 1.7% for samples and 1.4% for standards. Absolute deviation averaged less than 3.3% for all standards and quality control samples.

Stability Study

The concentrations of clozapine observed in the various suspensions over the study period are presented in Table 1 (as percentage of original concentration). During the study period, the concentration of clozapine in all study samples remained within 5% of the initial concentration, and the inter-day variation in clozapine concentration (as assessed by CV) was less than 2.5%.

On the basis of the 95% CI for the fastest degradation rate, all samples retained at least 93.97% of the initial concentration. Multiple linear regression detected a significant ($p = 0.0379$) trend for a change in concentration during the 63-day study period, but this change averaged only 2.56%. Analysis of variance did not reveal any significant difference between suspension vehicles in the percentage remaining ($p = 0.27$); the largest difference between any 2 vehicles, with 95% confidence (Ora-Plus and the 1:1 mixture of Ora-Sweet and Ora-Plus), was 5.16%.

Inspection of chromatograms obtained during the stability study revealed no increase in the concentration (peak height) of any degradation product or impurity that was observed during assay validation (Figure 2).

All suspensions were initially opaque and light creamy-white and remained so for the duration of the study. Caking of clozapine was not apparent in any of the containers, an observation supported by the concentration analysis.

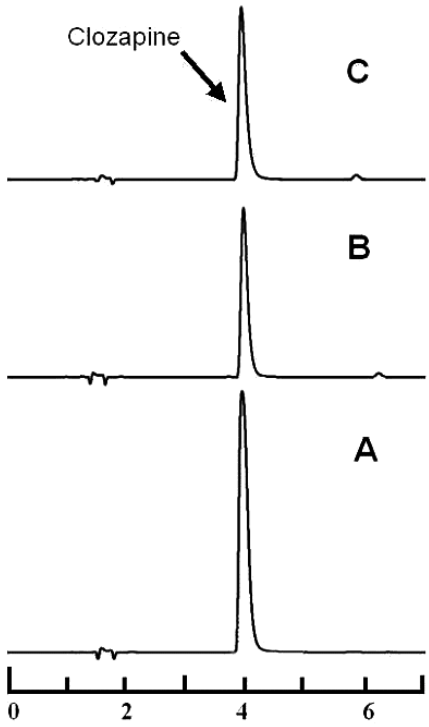

Figure 2. Representative chromatograms of clozapine in methanol (panel A) and during the stability study; panel B shows the chromatogram for a 20 mg/mL clozapine suspension in Guy's pediatric mixture on study day zero, and panel C shows the same suspension on study day 63. One of the degradation products or impurities identified during the accelerated degradation study (eluting at 6.4 min) was observed in the chromatograms for both study day zero and study day 63. However, this peak did not change during the study period, and no other peaks observed during the accelerated degradation study were observed in any sample during the stability study.

DISCUSSION

During the study period, the concentration of clozapine observed in all study samples remained within 5% of the initial concentration. Multiple linear regression detected a significant (p = 0.0379) trend for a change in concentration over the study period, but the change averaged only 2.56%. There were no significant differences in the rate of clozapine degradation among the suspension vehicles, and the lowest percentage of initial concentration remaining, estimated with 95% confidence on day 63, was 93.97%. Furthermore, degradation products observed during the accelerated degradation of clozapine were not observed during the stability study. Assuming no degradation and assuming that all concentration determinations represented estimates of an unchanging concentration, the inter-day reproducibility of sample concentrations was less than 1.7% (CV expressed as a percentage), which is similar to the error observed during the assay validation of quality control samples and standards (1.4%).

In considering extemporaneous formulation of a clozapine oral liquid, the authors set the following criteria for an acceptable formulation: palatable to patients; easily compounded, preferably using a commercially available suspending agent; stable for at least 60 days; and of sufficient concentration to avoid the need to administer large volumes. The suspending agents tested were Ora-Sweet, Ora-Plus, a 1:1 mixture of Ora-Sweet and Ora-Plus, the suspending vehicle used by the Hospital for Sick Children, simple syrup, and Guy's pediatric mixture. Ora-Sweet and Ora-Plus are commercially available suspending vehicles. Ora-Sweet is a mixture of sucrose, glycerin, and sorbitol, and Ora-Plus contains carboxymethyl cellulose, microcrystalline cellulose xanthan gum, and carrageen.[8] The Hospital for Sick Children's suspending vehicle is a methylcellulose and simple syrup mixture that is not commercially available and must be manufactured.[9] Similarly, Guy's pediatric mixture must be extemporaneously manufactured. Simple syrup is essentially a saturated solution of sucrose in water that is widely available from numerous distributors.

To properly evaluate the stability of a clozapine suspension, a suitable analytical method was required. Although a few publications have described analytical methods for measuring clozapine and its metabolites in biological samples,[10-12] the authors were aware of only one method for analyzing clozapine and its degradation products in pharmaceutical products.[13] However, even with the information from that publication, a stability-indicating analytical method for clozapine had to be developed and validated before the stability study could be initiated.[5-7] This analytical method was required to ensure that clozapine could be accurately and reproducibly measured in the presence of clozapine degradation products in different suspending agents.[14]

Because only small changes in clozapine concentration could be detected under the storage conditions studied, assurance of the specificity of the analytical method is very important. In addition, the separation and detection of intact drug in the presence of degradation compounds must be assured before the method can be considered suitable for indicating stability.[5-7] The specificity of the analytical method was demonstrated during the accelerated degradation studies (Figure 1). In these studies, the clozapine concentrations declined as the concentration of apparent degradation products increased.

Demonstrating a trend toward a substantial decline in concentration was considered more important than demonstrating a statistical difference in concentration between any 2 days. In fact, random fluctuations in concentration around the initial concentration are not of practical importance and should be considered "noise" or experimental error. Linear regression indicated that the concentration on day 63 was within 3% of the initial

concentration and that concentrations on day 63 would not be expected to fall below 93.97% of the initial clozapine concentration, with 95% confidence.

Given that the degradation rate or change in clozapine concentration over the 63-day study period did not differ among the suspending agents, the choice of an ideal suspending agent defaults to palatability and ease of preparation. Since both the suspending vehicle of the Hospital for Sick Children and Guy's pediatric mixture involve the time-consuming process of creating a methylcellulose solution, formulations using these vehicles cannot be considered ideal. Simple syrup is not as viscous as Ora-Sweet and Ora-Plus formulations and generally does not suspend particles as well. Furthermore, suspensions using simple syrup as the vehicle might be more prone to caking after standing for a prolonged period of time, although this problem was not observed in the current study. The Ora-Sweet and Ora-Plus vehicles do not present problems of preparation, suspension, or caking.

In conclusion, 20 mg/mL suspensions of clozapine prepared in Ora-Sweet, Ora-Plus, a 1:1 mixture of Ora-Sweet and Ora-Plus, the suspending vehicle of the Hospital of Sick Children, simple syrup, and Guy's pediatric mixture were stable insofar as they retained at least 93.97% of the initial clozapine concentration when stored in amber plastic containers at 23°C for 63 days. Because no difference in stability was observed with different suspending vehicles, the choice of suspending vehicle can be based on other variables such as cost, physical compatibility, availability, and patient preference. The authors consider the clozapine formulations prepared with commercially available Ora-Sweet or Ora-Plus products preferable to formulations prepared with the other vehicles and recommend these formulations because of their stability and ease of preparation.

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