Stability of Ketorolac Tromethamine in IV Solutions and Waste Reduction

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ABSTRACT

Objective: To evaluate the stability of ketorolac tromethamine during 21-day storage at 23°C and 4°C.

Methods: Solutions of ketorolac tromethamine (15 mg/50 mL and 30 mg/50 mL) were prepared and stored in polyvinylchloride (PVC) minibags at room temperature (23°C) and in the refrigerator (4°C). A validated, stability-indicating liquid chromatographic method was used to determine the concentration of the drug on each of 10 days over a 21-day storage period. Visual inspection and pH determinations were also completed on each of the study days.

Results: Over the study period, samples of both concentrations stored at either temperature retained more than 95% of the initial ketorolac concentration. The amounts of degradation products detected were insignificant.

Conclusions: Ketorolac tromethamine solutions of 15 mg/50 mL and 30 mg/50 mL (nominal concentrations of 0.3 and 0.6 mg/mL) stored in PVC minibags at 23°C and 4°C for 21 days were stable and retained more than 95% of the initial ketorolac concentration. The expiry period for such solutions may be extended to up to 21 days, as long as the sterility of the solutions is verified.

Key words: ketorolac, stability, wastage

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RÉSUMÉ

Objectif : Évaluer la stabilité de la trométhamine de kétorolac entreposée à des températures de 23 °C et de 4 °C pendant 21 jours.

Méthodes : Des solutions de trométhamine de kétorolac (15 mg/50 mL et 30 mg/50 mL) ont été préparées et conditionnées dans des minisacs de polychlorure de vinyle (PVC), puis entreposées à la température ambiante (23 °C) ou au réfrigérateur (4 °C). Outre l'inspection visuelle et la détermination du pH pour chaque jour de l'étude, la concentration en médicament a été déterminée à dix journées différentes durant la période d'entreposage de 21 jours, au moyen d'une épreuve de stabilité par chromatographie liquide à haute pression validée.

Résultats : Au cours de la période d'étude, des échantillons des deux concentrations entreposées à l'une ou l'autre température ont conservé plus de 95 % de leurs concentrations originales de kétorolac. La quantité de produits de dégradation décelée était non significative.

Conclusions : Les solutions de trométhamine de kétorolac préparées à raison de 15 mg/50 mL et de 30 mg/50 mL (concentrations nominales de 0,3 et de 0,6 mg/mL) et conservées dans des minisacs en PVC à des températures de 23 °C et de 4 °C durant 21 jours se sont révélées stables et ont retenu plus de 95 % de leurs concentrations originales de kétorolac. Les dates de péremption de telles solutions peuvent être prolongées jusqu'à 21 jours, en autant que la stérilité des solutions soit vérifiée.

Mots clés : kétorolac, stabilité, déperdition

INTRODUCTION

Ketorolac tromethamine (Toradol, Hoffmann - La Roche Ltd, Mississauga, Ontario) is a member of the pyrrolopyrrole group of nonsteroidal anti-inflammatory drugs. It is an effective inhibitor of prostaglandin synthesis and can be administered orally or intramuscularly.[1,2] It exhibits potent analgesic, anti-inflammatory, and antipyretic activity without opioid-related side effects[3–5] and may in fact be opioid-sparing.[3,4] Ketorolac is indicated for the short-term management of moderate to severe acute pain, including pain after major abdominal, orthopedic, and gynecological operative procedures.[2] In our institution, ketorolac has become popular as a postoperative analgesic agent.

Although ketorolac is approved for IM use, IV administration after orthopedic surgery has increased its use. There are no stability data for periods beyond 48 h for ketorolac diluted in IV fluids.[6] A common dosage regimen for ketorolac is 15 or 30 mg, administered every 12 h for 48 h. However, therapy is often discontinued after 24 h. As a result, because of both the high rate of discontinuation of therapy and the short expiry date, a significant amount of the drug was being wasted in our institution, and this had become an issue of concern.

Therefore, this study was undertaken to evaluate the stability of ketorolac in 0.9% sodium chloride in water (normal saline [NS]) or 5% dextrose in water (D5W), at concentrations of 15 and 30 mg in 50 mL. A validated, stability-indicating liquid chromatographic method was used to evaluate stability over a 21-day period at room temperature (23°C) and under refrigeration (4°C). Visual inspection and pH determinations were also completed on each of 10 study days during the 21-day storage period. As part of the investigation, the number of minibags prepared and wasted was monitored for 8 months before introducing a new expiry period and for 3 months after.

METHODS

Assay Validation — Specificity

Stability-indicating assay methods for ketorolac have been previously reported.[6–8] All 3 liquid chromatographic methods used a reverse-phase column with an acidic mobile phase and ultraviolet detection. Our method was similar and used an isocratic solvent delivery pump (model 510, Waters Corporation, Mississauga, Ontario), which pumped a mixture of acetonitrile (catalogue number AX0142-1, EM Science, Gibbstown, New Jersey) and phosphoric acid (0.05 mol/L, catalogue number P286, Fisher Scientific, Toronto, Ontario) through a 250 x 4.6 mm reverse-phase C_{18}, 5-μm column (Ultrasphere ODS [octadecylsilane] C_{18}; distributed in Canada by Beckman, Mississauga, Ontario) at 1.0 mL/min. The ratio of acetonitrile to phosphoric acid was 50:50 and was held constant during each chromatographic run. On each day the strength of the mobile phase was such that the retention time for ketorolac was between 330 and 390 s. Samples were introduced into the liquid chromatography system using an autoinjector (WISP 712, Waters Corporation, Toronto, Ontario). The column effluent was monitored with a variable-wavelength ultraviolet detector (Spectroflow 783 programmable absorbance detector, Kratos Analytical, Ramsey, New Jersey), set at 254 nm. A signal from the detector was integrated and recorded with a chromatography data system (PC 1000, Thermoquest, San Jose, California). The area under the ketorolac peak at 254 nm was subjected to least-squares linear regression, and the actual ketorolac concentration in each sample was determined by interpolation from the standard curve.

Assay Validation — Accuracy and Reproducibility

Once the chromatographic system for ketorolac had been set up, the suitability of this method for indicating stability was tested with degraded samples of ketorolac, prepared by accelerating the degradation process. A 1-mL sample of ketorolac tromethamine (Toradol 30 mg/mL, Hoffmann - La Roche Ltd, lot 80013, expiry January 2000) was diluted in 100 mL of distilled water. Solutions for analysis were prepared by mixing 10-mL samples of the 0.3 mg/mL stock solution with 2.0 mL of hydrochloric acid (6 mol/L, pH 0.74) or 1.0 mL of sodium hydroxide (10 mol/L, pH 13.15). These solutions were placed in glass vials and incubated in a water bath at approximately 90°C, protected from light. Samples were drawn just before incubation was started and at 7 other times over a 22-h period (16, 33, 48, 78, 104, 264 and 1321 min [22 h 1 min]). These samples were chromatographed, the chromatograms were inspected for the appearance of additional peaks, and the ketorolac peak was compared between samples for changes in concentration, retention time, and peak shape.

After this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over 5 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance. On each of the 5 days, 1 mL of ketorolac (30 mg/mL) was diluted in 30 mL of distilled water. Samples of this stock solution were further diluted with distilled water to obtain standards with final concentrations of 1.0, 0.8, 0.5, 0.4, 0.3, 0.2, and 0.1 mg/mL. When combined with a blank, these standards served to construct a standard curve. Twenty microlitres of each

sample was chromatographed (in duplicate). To check the accuracy of the standard curve, 3 quality control samples of ketorolac (concentrations 0.9, 0.6, and 0.15 mg/mL) were chromatographed in duplicate each day, with their concentrations determined and compared with the known concentrations. Within-day and between-day errors were assessed by the coefficients of variation of the peak areas of both quality control samples and standards.

Stability Study

On study day zero, 15 or 30 mg of ketorolac tromethamine (Hoffmann - La Roche Ltd, lot 80013) was added to each of 32 polyvinylchloride (PVC) minibags containing 50 mL of either 0.9% NS or D5W. The nominal concentration of ketorolac tromethamine in these minibags was 0.3 or 0.6 mg/mL. The nominal concentration did not take into account the approximately 10% of volume overfill or the volume added through the addition of ketorolac. Of the 32 minibags prepared, 16 contained 0.5 mL (15 mg) of ketorolac (8 each with NS and D5W), and the other 16 contained 1.0 mL (30 mg) (again, 8 each with NS and D5W). For each solution–concentration combination, half of the bags were stored at room temperature (23°C) and the other half in the refrigerator (4°C) for the duration of the study. In total, there were 4 bags for each solution–concentration–temperature combination. Three bags were used for the tests of chemical content and the fourth was used for pH tests and for visual inspection.

Ketorolac Analysis

On each study day (0, 1, 2, 7, 8, 9, 14, 15, 16, and 21), standard curves were prepared as described above. To check the accuracy of the standard curve, 3 quality control samples of ketorolac (concentrations of 0.9, 0.6, and 0.15 mg/mL) were prepared in a similar fashion and chromatographed in duplicate each day, with their concentrations determined and compared with the known concentrations. Within-day and between-day errors were assessed by the coefficients of variation of the peak areas of both quality control samples and standards.

Samples were drawn from each of the 24 minibags used for chemical analysis, and duplicate 20-μL samples of each were used for liquid chromatographic analysis on each of the 10 study days. The area under the ketorolac peak at 254 nm was subjected to least-squares linear regression, and the actual concentration of ketorolac tromethamine in each sample was determined by interpolation from the standard curve. Ketorolac concentrations were recorded to the nearest 0.001 mg/mL.

The concentrations of the degradation products of ketorolac could not be measured because of the lack of standards for each of these degradation products. Instead, the peak area of one of the degradation products was monitored daily and compared between days for changes.

Visual Inspection and Determination of pH

Solutions were inspected visually as they were drawn for pH analysis. On each of the 10 study days, a sample was drawn, placed in a 10 x 75 mm glass test tube and inspected visually for colour and clarity against a black background and a white background under normal diffuse fluorescent laboratory light. The pH of each solution was then measured and recorded to the nearest 0.001 unit. The pH meter (Accumet model 925, Fisher Scientific, Toronto, Ontario) was equipped with a microprobe glass-body electrode (catalogue number 13-639-280, Fisher Scientific, Toronto, Ontario). Before and after the pH measurements, the pH of a reference solution was measured and recorded to assure accuracy of the pH measurements.

Preparation of Drug and Monitoring of Wastage

Daily preparation records for the inpatient IV additive system were monitored between October 1997 and August 1998, and the dose and number of ketorolac minibags recorded. The number of bags with ketorolac concentrations of 15 mg/50 mL and 30 mg/50 mL were tabulated daily, as was the total quantity of drug (in milligrams) prepared each day. The monthly departmental records of wastage were also monitored, and the number of bags (both 15 mg/50 mL and 30 mg/50 mL) destroyed was tabulated over the same period. These records allowed calculation of the number of bags and total quantity of drug (in milligrams) prepared, used, and wasted. Wastage was calculated as the quantity of drug discarded per month (in milligrams) divided by the quantity of drug sent to the wards (also in milligrams), expressed as a percentage.

Data Reduction and Statistical Analysis

Means were calculated for analyses completed in duplicate and triplicate. Error was assessed by the coefficient of variation (the standard deviation divided by the mean). Mean concentrations for different days were compared statistically by least-squares multiple linear regression, where factors in the model include IV solution, temperature, and study day, to determine if there was an association between concentration and study day. Analysis of variance and the least significant

difference multiple-range test were used to compare differences in concentration between days, with the factors of IV solution, temperature, and study day (as "time") included in the error model. Log–linear and linear–linear fits for the data from the accelerated degradation study (with hydrochloric acid and sodium hydroxide at 90°C) were compared for goodness of fit by the maximum likelihood method of Box and Cox.[9,10] The mean amounts of ketorolac prepared, used, and wasted before and after the study were compared by an unpaired Student's *t*-test, with the assumption of equal variance and use of confidence intervals. The 5% level was used as the a priori cutoff for significance, and all references to significance refer to this level.

Ketorolac tromethamine concentrations were considered "acceptable" or "within acceptable limits" if the concentration on any day of analysis did not deviate by more than 10% from the initial (day zero) concentration.

RESULTS

Accelerated Degradation and Assay Validation

The degradation of ketorolac was dependent on pH. At a pH of 13.15 (with sodium hydroxide) and a temperature of 90°C, virtually all of the ketorolac was lost before the time zero sample was assayed (within 15 min). At least 2 degradation products eluted very near the solvent front, and neither would have interfered with quantification of ketorolac. At a pH of 0.74 (with hydrochloric acid) and a temperature of 90°C, approximately 94% of the ketorolac was lost over the 22-h study period. This corresponds to a half-life of 11.7 h under these conditions, and these data were fit significantly better by a first-order rate (r value for first-order rate = 0.9988 and for zero-order rate = 0.9206). At least 2 degradation products were observed in the chromatograms (Figure 1). Neither of these degradation products, which had different retention times from those of the products observed after degradation with base, interfered with quantification of ketorolac. As a result of the predictable degradation of ketorolac over the first 22 h and the chromatographic separation of all degradation products from ketorolac, it was concluded that this analytical method was suitable for indicating stability.[11,12]

Analysis of the evaluations of accuracy and reproducibility indicated that the ketorolac concentration was measured accurately. Determinations of accuracy, based on the mean of duplicate determinations of standards over the study period, showed less than 4.63% deviation from theoretical concentrations, and deviation from the expected concentration of the 3 quality control samples averaged less than 3.63%. Analytical reproducibility, within a day (as measured by the coefficient of variation), averaged less than 0.44% for each of the 7 standards and the 3 quality control samples. This indicates that differences of 10% or more could be confidently detected with acceptable error rates.[13] System suitability criteria were developed on the basis of daily calculations of theoretical plates, tailing, retention time, and accuracy observed during the validation period and were used to ensure continued chromatographic performance during the study period.

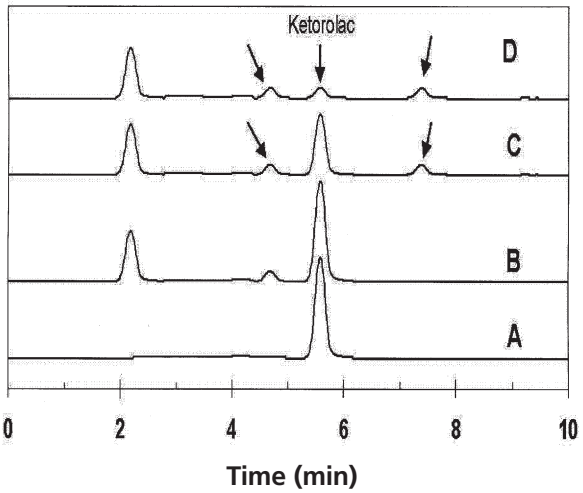

Figure 1. Representative chromatograms of ketorolac in normal saline (A) and during the accelerated study at a pH of 0.74 and a temperature of 90°C (B, C, and D). Two potential degradation products were eluted, with retention times of 4.7 and 7.3 min, respectively. Neither was positively identified. Chromatogram B represents a sample drawn at time zero in the accelerated study, chromatogram C represents a sample drawn after 264 min (4 h 24 min), and chromatogram D represents a sample drawn after 1321 min (22 h 1 min), when only 6.24% of the initial concentration of ketorolac remained.

Stability Study

Ketorolac tromethamine did not degrade appreciably over the study period at either temperature. The mean percentage remaining for each combination of IV solution, nominal concentration, and temperature on each study day is given in Table 1. Over the 21-day study period the ketorolac concentration in the 15 mg/50 mL bags ranged from 97.40% to 101.75% (average 99.49%, coefficient of variation 1.08%) and in the 30 mg/50 mL bags, the concentration ranged from 97.38% to 103.57% (average 99.86%, coefficient of variation 1.25%). Analysis of variance was able to detect statistically significant differences in concentration due to IV solution (p = 0.0409), nominal concentration (p = 0.0187), temperature (p = 0.0001), and study day (p = 0.0203). However, all of the differences between

Table 1. Mean Percentage of Ketorolac Concentration* ± Standard Deviation Remaining during 21 Days of Storage at 4°C and 23°C

	15 mg/50 mL NS†		30 mg/ 50 mL NS†		15 mg/50 mL D5W†		30 mg/50 mL D5W†	
Study day	**23°C**	**4°C**	**23°C**	**4°C**	**23°C**	**4°C**	**23°C**	**4°C**
0*	0.24 ± 0.01	0.24 ± 0.01	0.55 ± 0.02	0.53 ± 0.03	0.27 ± 0.01	0.28 ± 0.01	0.49 ± 0.01	0.55 ± 0.01
1	100.39 ± 0.09	100.16 ± 0.05	99.88 ± 0.07	100.05 ± 0.02	100.19 ± 0.06	99.65 ± 0.10	99.22 ± 0.02	99.83 ± 0.03
2	99.31 ± 0.07	99.75 ± 0.07	99.74 ± 0.06	99.27 ± 0.07	98.94 ± 0.02	99.07 ± 0.03	98.77 ± 0.04	99.38 ± 0.01
7	99.21 ± 0.03	99.12 ± 0.06	99.15 ± 0.07	98.31 ± 0.06	98.57 ± 0.05	97.55 ± 0.04	99.12 ± 0.03	98.18 ± 0.02
8	100.32 ± 0.04	98.74 ± 0.02	100.77 ± 0.07	99.11 ± 0.05	99.00 ± 0.04	97.63 ± 0.06	100.11 ± 0.01	98.89 ± 0.12
9	98.97 ± 0.08	97.46 ± 0.11	98.95 ± 0.03	97.38 ± 0.08	97.88 ± 0.03	97.40 ± 0.02	98.70 ± 0.11	97.60 ± 0.04
14	101.75 ± 0.12	100.14 ± 0.06	102.16 ± 0.04	100.99 ± 0.02	101.35 ± 0.04	100.06 ± 0.08	101.79 ± 0.08	101.07 ± 0.07
15	101.47 ± 0.02	99.56 ± 0.02	103.57 ± 0.05	101.37 ± 0.06	100.68 ± 0.05	99.94 ± 0.02	101.63 ± 0.07	100.99 ± 0.04
16	98.45 ± 0.06	99.98 ± 0.08	100.65 ± 0.03	100.06 ± 0.10	100.99 ± 0.01	100.07 ± 0.10	100.93 ± 0.07	100.35 ± 0.09
21	100.41 ± 0.10	98.25 ± 0.04	100.44 ± 0.01	98.03 ± 0.02	99.43 ± 0.03	97.69 ± 0.06	99.54 ± 0.06	98.32 ± 0.07
% remaining on day 21 by linear regression‡	100.68	99.19	102.06	100.03	101.01	99.65	101.70	100.26
Lower 95% CL for % remaining§	98.15	97.07	99.09	96.92	98.39	96.76	99.32	97.36

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, CL = confidence limit.

* For each combination of IV solution, nominal concentration, and temperature, a sample was drawn from each of 3 minibags, and concentration was determined in duplicate (for a total of 6 concentration estimates). The mean of the duplicate values was determined, and then the overall mean for the 3 samples was calculated. The initial concentration (day zero) is reported in milligrams per millilitre, and the percentage remaining was calculated in relation to this initial concentration.

† Solutions were prepared by adding 1.0 or 0.5 mL of ketorolac tromethamine (30 mg/mL) to a 50-mL polyvinylchloride minibag. The nominal concentration of these solutions was 0.3 or 0.6 mg/mL. The nominal concentration does not take into account the approximately 10% volume overfill or the volume added through the addition of ketorolac. This overfill explains the difference between the expected concentrations of 0.3 and 0.6 mg/mL and the observed concentrations of about 0.25 and 0.50 mg/mL, respectively.

‡ Calculated from concentration on day 21 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 21/concentration on day zero x 100.

§ Calculated from lower limit of 95% confidence interval of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of 95% confidence interval of concentration on day 21/concentration on day zero x 100.

means were less than 1%, and differences this small are generally considered clinically unimportant. Multiple linear regression was also able to detect a significant association between concentration and IV solution (p = 0.0406), nominal concentration (p = 0.0186), temperature (p = 0.0001), and study day (p = 0.0216), but again the differences represented changes of less than 1% and were not clinically important. Furthermore, the percentage remaining on day 21 was within 2% of the day 0 concentration (Table 1), and the lower 95% confidence limit for the percentage remaining on day 21 was at least 96.76% for all combinations of IV solution, nominal concentration, and temperature.

Inspection of the chromatograms during the stability study failed to reveal significant amounts of the degradation products that were observed during the accelerated degradation phase of the study (Figure 1, chromatograms B, C, and D). The chromatograms did demonstrate some evidence of the presence of impurities; however, these contaminants did not change in concentration over the study period. Because of the failure to detect any degradation products, confident estimates of the degradation rate could not be determined for ketorolac at either temperature. All solutions remained clear and colourless. The pH values ranged from 5.66 to 6.84, and stayed relatively constant over the course of the study (coefficient of variation less than 5%).

Wastage

In June 1998, the expiry period for ketorolac was changed from 48 h to 7 days. Data on ketorolac prepared, used, and wasted before and after the change in expiry period are presented in Table 2. In the 3 months after the change, there was an insignificant reduction in the amount of ketorolac prepared (p = 0.638). After the change, the amount of ketorolac wasted was reduced by nearly 80%, from an average of 1601.9 mg/month to an average of 324.3 mg/month (p = 0.000008). Although the percentage wasted varied considerably between October 1997 and May 1998 (from 22.2% to 52.8%), it was significantly lower after introduction of the new expiry period (Table 2). Over

Table 2. Wastage of Ketorolac* from October 1997 to August 1998†

Month	Total Quantity Prepared (mg)	Total Quantity Discarded (mg)	Total Quantity Used (mg)	Wastage (%)
Before new expiry period				
October 1997	3780	1410	2370	37.3
November 1997	6810	1515	5295	22.2
December 1997	4030	1425	2605	35.4
January 1998	3465	1830	1635	52.8
February 1998	4455	2045	2410	45.9
March 1998	4320	1620	2700	37.5
April 1998	6390	1515	4875	23.7
May 1998	3960	1455	2505	36.7
Summary data				
Mean	4651.3	1601.9	3049.4	36.44
Standard deviation	1245.7	224.7	1301.8	10.17
Coefficient of variation (%)	26.8	14.0	42.7	27.91
Upper 95% confidence limit	5863.3	1820.5	4316.0	46.34
Lower 95% confidence limit	3439.3	1383.2	1782.8	26.55
After new expiry period				
June 1998	4725	255	4470	5.4
July 1998	4440	195	4245	4.4
August 1998	4829	523	4306	10.8
Summary data				
Mean	4664.7	324.3	4340.3	6.87
Standard deviation	201.4	174.7	116.4	3.46
Coefficient of variation (%)	4.3	53.9	2.7	50.40
Upper 95% confidence limit	4860.6	494.3	4453.6	10.24
Lower 95% confidence limit	4468.7	154.4	4227.1	3.50
Comparison				
Ratio of variance	38.25	1.66	125.15	8.62
p value (*t*-test)	0.9861	<0.0001	0.1315	0.0010

* At Sunnybrook Health Science Centre, now Sunnybrook and Women's College Health Science Centre.

† Data were compiled from the daily records of the Pharmacy Manufacturing Group and were converted from number of bags to total amount of drug (in milligrams). The records were separated into 2 groups: before and after the introduction of the new expiry period.

the 8 months before the change in expiry period, a total of 12 815 mg (or 34.4% of the ketorolac prepared) was wasted. At the prevailing price at the time ($20.65 for five 1-mL ampoules of 30 mg/mL), the cost of this waste was approximately $220/month and the savings through reduced wastage was about $177/month (based on average amount wasted). However, this calculation does not account for the cost of labour or materials, which were estimated in 1987 to be approximately $1.00 and $1.20 (label and minibag) per unit, respectively.[14]

DISCUSSION

Although analysis of variance of the ketorolac concentration data in this study detected the significance of differences as small as 1%, demonstrating a trend for the concentration to decrease was considered more important than demonstrating a statistical difference in concentration between any 2 days. In fact, the 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 21 was within 2% of the initial concentration and that deviations on any day did not exceed 3%. Assuming no degradation and assuming that determinations on all study days represented estimates of an unchanging concentration, the between-day reproducibility can be calculated as 1.16% (coefficient of variation expressed as a percentage), which is equivalent to the error observed during the assay validation of quality control samples and standards.

Because only small changes in ketorolac concentration could be detected under these storage conditions, assurance of the specificity of the analytical method is very important. The specificity of the analytical method was demonstrated during the accelerated degradation studies (Figure 1). In these studies reduced ketorolac concentrations were measured as the concentration of apparent degradation products increased. 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.[11,12]

Because there was no concurrent control during the evaluation of wastage, it was difficult to determine if

some other factor coincidentally reduced the wastage. However, the high rate of wastage was a problem of which the department was acutely aware, and after high rates of wastage were observed in January and February 1998, special procedures were introduced in an attempt to reduce this wastage. Initially, pharmacy assistants were instructed to inspect wards known to use ketorolac and to recover minibags immediately after ketorolac was discontinued. This procedure was introduced in March 1998, and although it was apparently moderately successful, wastage still exceeded 20% over the next 3 months (March to May 1998). However, after the introduction of the longer expiry period, the increased vigilance of the pharmacy assistants in recovering minibags from the wards was discontinued and wastage was still reduced to less than 10%.

Expiry dating is only one factor influencing wastage of an IV additive.[14,15] The rate of use of the drug and the frequency between orders is also important. If a medication is used infrequently, extending the expiry period may not reduce wastage, since it may not be possible to administer the product to the next patient before expiration.[15] Therefore, the reduction in wastage of ketorolac in our hospital was a result of both the extension of the expiry period to 7 days, the high rate of use of this drug, and our policy of allowing IV medications to be "recycled" at least twice before being destroyed. Extension of the expiry period beyond 7 days was not considered necessary because it has been previously noted that for frequently prescribed antibiotics, wastage could be reduced to less than 5% with a 7-day shelf life.[14]

It is concluded that ketorolac solutions of 0.3 mg/mL (15 mg/50 mL) and 0.6 mg/mL (30 mg/50 mL) in either NS or D5W, stored at 23°C and 4°C for 21 days, are stable and retain more than 95% of the initial ketorolac concentration during the storage period. If ketorolac is used frequently, extension of the expiry period to 7 days may be sufficient to reduce wastage to minimal levels. However, the actual expiry date used in any institution should be established only after consideration of both the bacterial contamination rate for the IV additive service and stability data.

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