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Incompatibility of cisplatin and Reglan Injectable

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Summary

The stability of cisplatin (*cis*-diamminedichloroplatinum (II)) in solutions containing Reglan Injectable, comprised of metoclopramide, sodium metabisulfite and sodium chloride, was examined. Loss of cisplatin was monitored by measuring the increasing chloride ion concentrations with a chloride ion-specific electrode. Cisplatin was stable in solution with metoclopramide alone, but degraded very rapidly in solution with metabisulfite. At concentrations similar to those which might be expected in clinical situations (cisplatin = 0.2 mg/ml, metabisulfite = 0.148 mg/ml, metoclopramide = 0.5 mg/ml) there was total loss of cisplatin within 30 min at room temperature. The results indicate that cisplatin reacts with species formed in the oxidation of bisulfite. Therefore, cisplatin should not be admixed with Reglan Injectable solution or any solution containing bisulfite or chemically related antioxidants.

Introduction

Cisplatin (*cis*-diamminedichloroplatinum (II)) is a widely used antineoplastic agent. Among the toxicities of cisplatin are severe nausea and vomiting (Schurig et al., 1980) which often cause patients to discontinue therapy which might otherwise be quite effective. Several studies (Gralla et al., 1981a and b; Strum et al., 1982;

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Daniels and Belt, 1982) have identified intravenous metoclopramide (Reglan Injectable) as an effective agent for controlling cisplatin-induced nausea and vomiting. The antiemetic regimens used in those studies employed high doses of metoclopramide given intravenously in several separate infusions. Through personal communications with clinicians and representatives of Bristol Laboratories (suppliers of cisplatin (Platinol)) and A.H. Robins (suppliers of Reglan) we have become aware of situations in which cisplatin and Reglan Injectable might be admixed in a single parenteral fluid. To date there has been no publication of results of compatibility studies for such an admixture although these authors have communicated with two institutions which have looked at this problem and were unable to detect evidence of incompatibility.

In view of the reported reaction of cisplatin with bisulfite (Hussain et al., 1980) and other nucleophiles (Riley et al., 1982) and the fact that Reglan Injectable contains the potential nucleophiles, metoclopramide and sodium metabisulfite, a compound which is rapidly hydrolyzed in aqueous solution to bisulfite (Schroeter, 1961), this study was undertaken. The purpose was to assess the stability of cisplatin in aqueous solutions containing Reglan Injectable.

Materials and Methods

Cisplatin (NSC Lot No. 119875-MC) was obtained from the National Cancer Institute (Bethesda, MD 20014) and used as received. Bulk metoclopramide-HCl monohydrate (AHR-3070C) was obtained from A.H. Robins (Richmond, VA 23220). Reglan Injectable (2-ml vials, A.H. Robins, Richmond, VA 23220) was obtained from a local hospital. All other compounds were reagent grade and used as received.

The free base of metoclopramide was prepared by dissolving ≈ 1 g of metoclopramide hydrochloride in 20 ml of distilled water. Aqueous sodium hydroxide (10 N) was added until the resulting solution was pH ≈ 12 and a white precipitate was observed. This suspension was extracted with ether (4×100 ml). The ether fractions were combined and residual water was removed by filtration through anhydrous sodium sulfate. The ether was evaporated leaving a white powder. The characteristics of the isolated solid were in good agreement with literature values for metoclopramide free base: mp 146–149°C (lit. mp 146.5–148°C) (Pakula et al., 1980), elemental analysis, calcd. C = 56.09%, H = 7.40%, N = 14.02%; and found C = 56.42%, H = 7.49%, N = 13.96%.

Loss of cisplatin in the reaction mixtures was monitored by following increasing chloride ion concentrations with a chloride ion-specific electrode (Orion Research, Cambridge, MA 02139; Model 9417B) in conjuction with a standard reference electrode (Corning Scientific, Medfield, MA 02052; Model 476109). Potential measurements were made with a standard pH meter (Corning Scientific, Medfield, MA 02052; Model 110). The reaction mixtures were monitored under ambient conditions (T = 18–21°C) and were well-stirred throughout the experiments. The desired pH was maintained through the use of citrate buffer (0.20 M) prepared with distilled water. The reaction mixtures (total volume of 5 ml) were prepared in 20 ml beakers.

The electrodes were immersed in the solution and readings were taken immediately upon initiation of the reaction. The chloride ion electrode calibration curve was linear ($r = 0.99$) over the range from $\approx 10^{-4}$ M to 0.1 M.

Ultraviolet spectrophotometry experiments were done using a model 555 spectrophotometer (Perkin-Elmer, Oak Brook, IL 60521) equipped with a digital temperature-controller (Perkin-Elmer, Oak Brook, IL 60521; Model 5700701). The temperature was maintained at 25°C. The reaction mixtures were prepared in the spectrophotometer cells. The reactions were initiated and the cells inverted two or three times for mixing. Absorbance was monitored beginning at 10 s after initiation of the reaction. Absorbance changes in solutions of cisplatin and sodium metabisulfite were monitored at 300 nm and solutions containing other compounds in addition to cisplatin and sodium metabisulfite were monitored at 350 nm.

The HPLC system used a solvent-generated anion exchanger similar to that described by Riley et al. (1981). The mobile phase contained 10^{-4} M hexadecyltrimethylammonium bromide and 0.01 M phosphate buffer, pH = 7.50. The flow rate was 1 ml/min and detection was at 280 nm.

Results and Discussion

Initial experiments showed that mixing cisplatin solution (1 mg/ml = 3.33×10^{-3} M, 0.1 N NaCl) of pH ≈ 6 with Reglan Injectable solution of pH ≈ 4 resulted in a solution with pH < 3 which was well below that expected (4 < pH < 6). Additionally when cisplatin (3.33×10^{-3} M) was mixed with sodium metabisulfite (2.38 mg/ml = 1.25×10^{-2} M) in an aqueous solution containing 0.1 N NaCl there was a rapid increase in absorbance at 350 nm, similar to that reported by Hussain et al. (1980). Continuous monitoring of the pH of this solution showed a rapid decrease in pH, the rate of which correlated well with the rate of increase in absorbance in this system. Upon incorporation of metoclopramide-HCl (4.5 mg/ml = 1.27×10^{-2} M) to the cisplatin–metabisulfite system, there was no change in absorbance at 350 nm, but the rate and extent of change of pH was similar to that seen without metoclopramide-HCl. HPLC methods showed that there was rapid loss of cisplatin (initial concentration = 3.33×10^{-3} M) when it was mixed in solution with sodium metabisulfite (7.79×10^{-3} M). At pH values within the range of 3–6, all of the cisplatin was lost within 10 min after addition of sodium metabisulfite.

HPLC analysis of solutions prepared by dissolving cisplatin directly in Reglan Injectable yielded results which appeared to suggest that metoclopramide inhibited the reaction of cisplatin with metabisulfite. However, close inspection of the HPLC data revealed that the components of Reglan Injectable produced a loss of resolution leading to a virtual co-elution of cisplatin and one of its reaction products. It was also noted that repeated injection caused continual chromatographic deterioration and attempts to modify the HPLC procedure to obviate the problem were unsuccessful.

Accordingly, HPLC was not useful in assessing the stability of cisplatin in solutions containing Reglan Injectable. While the results of the pH and spectropho-

tometric experiments indicated that some reaction was occurring, they again provided no definitive information regarding the integrity of the cisplatin molecule. Consequently it was necessary to identify another analytical procedure to assess the stability of cisplatin.

Since cisplatin is known to undergo reactions in which displacement of chloride ligands occurs (Basolo and Pearson, 1967), the formation of chloride ion in solutions containing cisplatin would be a direct measure of rate and extent of loss of intact cisplatin. While the chloride specific electrode is an obvious tool for that purpose, its sensitivity necessitated that solutions initially be largely chloride ion-free. The reaction mixtures used in the chloride ion-detecting experiments were prepared chloride-free by using the free base of metoclopramide and buffer solutions containing no chloride ion.

Fig. 1 shows the effect of pH on the rate of formation of chloride ion in solutions containing cisplatin (1.67×10^{-3} M) and sodium metabisulfite (1.25×10^{-2} M). The rate of formation of chloride ion correlated well with the changes in pH and absorbance at 350 nm seen previously. At all three pH values the final concentration of chloride ion achieved was twice that of the initial cisplatin concentration indicating that both chloride ligands were displaced from the cisplatin molecule. When cisplatin (1.67×10^{-3} M) was mixed in solution with metoclopramide free base (1.50×10^{-2} M) there was essentially no increase in chloride ion concentration on the time scale of Fig. 1. Over an extended period the rate of formation of chloride ion was not significantly different than control solutions of cisplatin in distilled

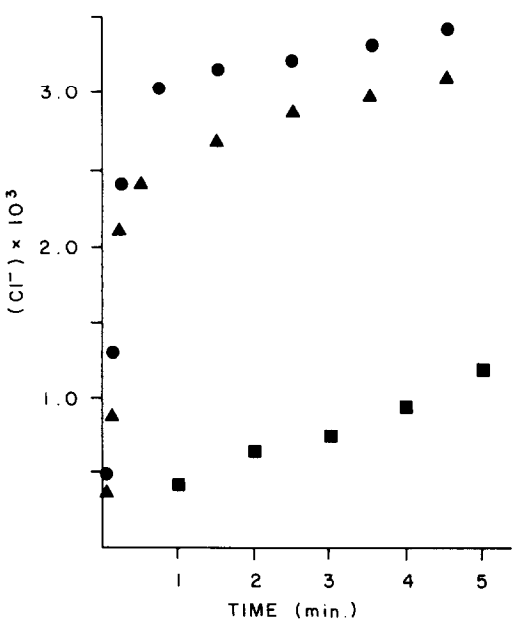
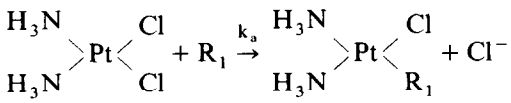


Fig. 1. Formation of chloride ion in citrate buffer (0.20 M) solution containing 1.67×10^{-3} M cisplatin and 12.5×10^{-3} M sodium metabisulfite. ●, pH = 6.0; ▲, pH = 4.5; ■, pH = 3.0.

water alone, where extensive aquation of cisplatin occurs (Hincal et al., 1979). It was also previously shown (Hincal et al., 1979) that the stability of cisplatin in aqueous solution is enhanced by the presence of chloride ion. In the present study it was observed that the rates and nature of the changes in pH and absorbance which occurred in solutions containing 0.1 N NaCl correlated well with formation of chloride ion in the 'chloride-free' systems, providing evidence that cisplatin is lost upon reaction with bisulfite even in the presence of chloride ion.

Inclusion of metoclopramide free base (1.50×10^{-2} M) in the reaction mixture with cisplatin (1.67×10^{-3} M) and sodium metabisulfite (1.25×10^{-2} M) had a minor effect on the kinetics of formation of chloride ion at pH 3.00 (Fig. 2). The formation of chloride ion appeared to proceed in two steps. There was an initial rapid rise in the chloride ion concentration to a level equivalent to the initial molar concentration of cisplatin. The reaction then continued at a slower rate to a final level equivalent to twice the initial cisplatin concentration. These data suggest a sequential process as shown in Eqns. 1 and 2, where R_1 and R_2 are reactants the nature and source of which are addressed below. In accord with Eqn. 1 the formation of one molar equivalent of chloride ion indicates total loss of cisplatin.



(1)

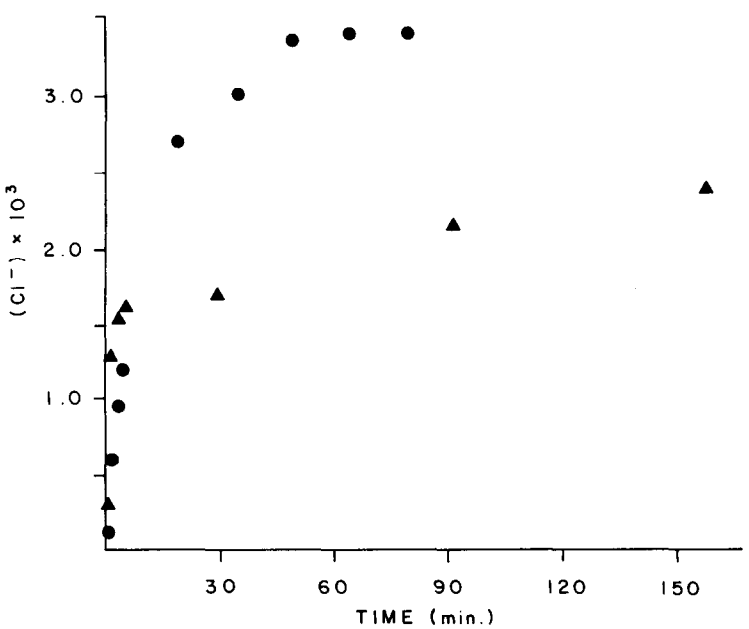


Fig. 2. Formation of chloride ion in citrate buffer (0.20 M, pH = 3.0) containing 1.67×10^{-3} M cisplatin and 12.5×10^{-3} M sodium metabisulfite with (▲) and without (●) metoclopramide base (0.015 M).

$$\begin{matrix} H_3N & & Cl \\ & \rangle Pt \langle & \\ H_3N & & R_1 \end{matrix} + R_2 \xrightarrow{k_b} \begin{matrix} H_3N & & R_2 \\ & \rangle Pt \langle & \\ H_3N & & R_1 \end{matrix} + Cl^- \qquad (2)$$

The concentrations of the reactants in the experiments described above are much higher than those expected in a typical admixture which might be used clinically. Under conditions which might be encountered in a clinical situation (cisplatin = 0.2 mg/ml (6.66×10^{-4} M), metoclopramide = 0.5 mg/ml (1.67×10^{-3} M), sodium metabisulfite = 0.148 mg/ml (7.79×10^{-4} M)) the rate of chloride ion formation was slower than the previous cases, as would be expected. The chloride ion reached a level equivalent to the initial cisplatin concentration (i.e. total loss of cisplatin) in 30 min as compared to ≈ 5 min at the higher concentrations. The pH of the solution was observed to decrease significantly from pH ≈ 5 to pH ≈ 4 over this time period. Although the loss of cisplatin was slower at this lower concentration it was still so rapid that such an admixture would be clinically unacceptable since $\geq 10\%$ drug loss would be expected in < 5 min. Lower concentrations of the reactants were not studied due to inadequate sensitivity of the chloride electrode and insufficient changes in pH at cisplatin concentrations less than 10^{-4} M.

It has previously been shown that bisulfite undergoes oxidation by a free radical process (Schroeter, 1961). Hussain et al. (1980) suggested the possibility of a free

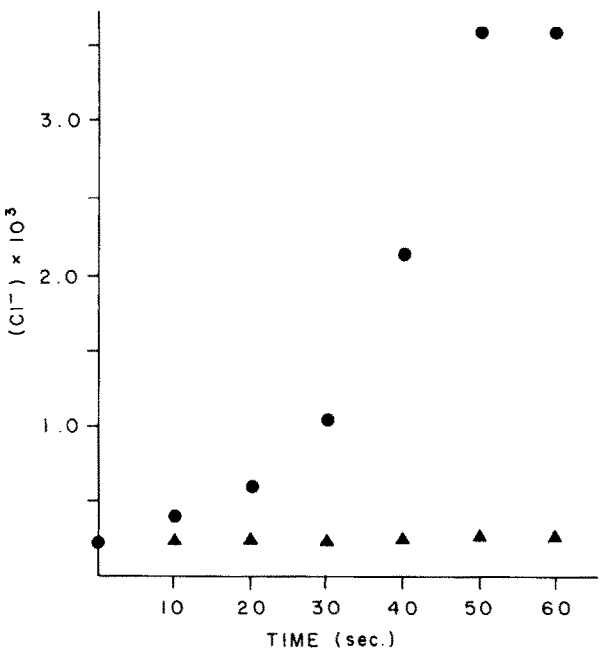


Fig. 3. Formation of chloride ion in solutions containing 3.33×10^{-3} M cisplatin and 12.5×10^{-3} M sodium metabisulfite with (▲) and without (●) hydroquinone (0.015 M).

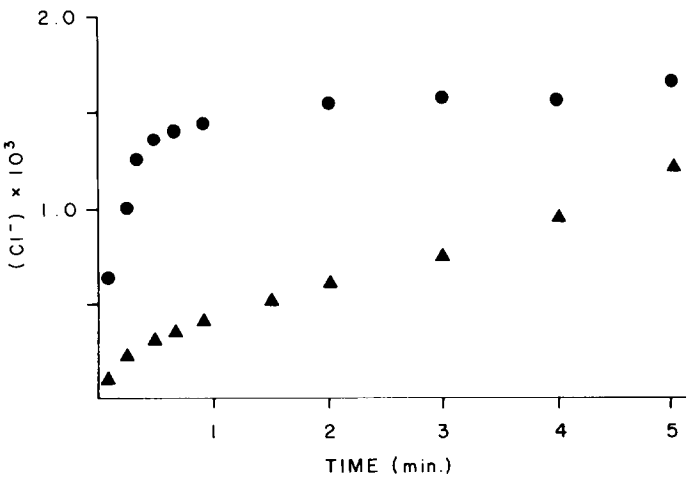
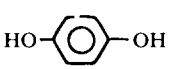
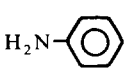
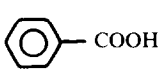
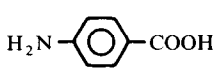
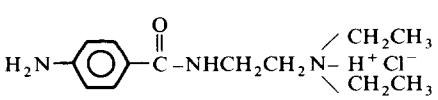
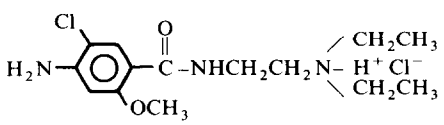


Fig. 4. Formation of chloride ion in 0.20 M citrate buffer (pH = 3.00) containing 1.67×10^{-3} M cisplatin and 12.5×10^{-3} M sodium metabisulfite with (●) and without (▲) hydrogen peroxide (0.015 M).

TABLE 1

EFFECT OF VARIOUS COMPOUNDS ON THE CHANGE IN ABSORBANCE (350 nm) OF CISPLATIN–METABISULFITE SYSTEM [a]

Compound [b]	Structure	% absorbance change
None	–	100
Methanol	CH_3OH	50
Hydroquinone		0
Aniline		10
Benzoic acid		50
p-Aminobenzoic acid		0
Procaine HCl		0
Metoclopramide HCl		0

[a] Cisplatin (3.33×10^{-3} M), sodium metabisulfite (12.5×10^{-3} M), sodium chloride (0.1 N), in citrate buffer (0.05 M, pH = 3.0).
[b] 0.015 M.

radical process being involved in the reaction of cisplatin with bisulfite due to the lag time and sigmoidal shape of the absorbance vs. time curve. The possibility of a free radical process being involved in the reaction of cisplatin with metabisulfite was studied by addition of either a known free radical scavenger (hydroquinone) or a known enhancer of free radical reactions (hydrogen peroxide) to reaction mixtures of cisplatin and sodium metabisulfite (Figs. 3 and 4). Hydroquinone inhibited the rate of chloride ion formation while hydrogen peroxide accelerated the process. These results suggest that a free radical process is involved in the reaction of cisplatin with metabisulfite. It appears probable that either R_1 and/or R_2 (Eqns. 1 and 2) may be bisulfite-derived free radicals formed during the oxidation of bisulfite. Ultraviolet spectrophotometry showed that the increase in absorbance at 350 nm was inhibited by various compounds capable of acting as free radical scavengers (see Table 1). The results suggest that the aryl amino group of metoclopramide may be largely responsible for inhibiting the increase in absorbance. However, as mentioned previously, in the case of metoclopramide there was formation of chloride ion under the same conditions. Thus while absorbance changes were inhibited, loss of cisplatin was not. Consequently, the change in absorbance does not accurately reflect the stability of cisplatin in the system.

Conclusions

Some important observations made in this study were: (1) the rate of loss of cisplatin with bisulfite in the presence of chloride ion is faster than the loss of cisplatin in the presence of chloride ion alone as determined by HPLC; (2) in cisplatin–bisulfite solutions initially containing no free chloride ion the presence or absence of metoclopramide had no effect on the rate of production of chloride ion up to a molar concentration equal to the initial cisplatin concentration; (3) the presence of metoclopramide had no effect on the rate and extent of pH change upon admixture of cisplatin and bisulfite solutions; and (4) in the absence of bisulfite, the rate of chloride ion production in cisplatin solutions initially containing no free chloride ion was unaffected by the present or absence of metoclopramide.

From these observations it is clear that cisplatin is incompatible with Reglan Injectable. However, such incompatibility is due to the bisulfite rather than the metoclopramide in Reglan Injectable. Additionally, results obtained in this study appear to provide strong evidence that a free radical process is involved in the reaction of cisplatin with metabisulfite.

Because of the reactive nature of cisplatin toward many nucleophiles (Hussain et al., 1980; Riley et al., 1982) and the complexity of drug formulations it may be concluded that cisplatin should not be admixed with any other drug formulations unless careful and appropriate stability studies have clearly demonstrated absence of any physical and chemical incompatibilities.

Since cisplatin loss was found to be affected significantly only by the metabisulfite contained in Reglan Injectable solution, the problem might be obviated by reformulation of Reglan Injectable. Substitution of a non-reactive antioxidant for

the metabisulfite, or simple deletion of the antioxidant (if metoclopramide was sufficiently stable in the absence of an antioxidant) are possible avenues which might be considered.

Finally, this study has demonstrated: (a) the importance of considering not only the compatibility of drug molecules with each other, but also with excipients present in an intravenous admixture; and (b) the need for proper selection and evaluation of the analytical methodology in assessing stability and incompatibility of cisplatin.

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