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Review

A review of the stability and compatibility of antineoplastic drugs for multiple-drug infusions

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Summary. It is important that the stability of reconstituted parenteral antineoplastic agents be established, particularly in the context of ambulatory infusion systems for delivery. The stability of selected agents within each of the five classes of compounds (antimetabolites, alkylating agents, antibiotics, alkaloids and glycosides, and metals) is reviewed from the literature together with additional data from studies carried out using high-performance liquid chromatographic (HPLC) technology in clinically applicable volumes and concentrations for ambulatory infusion. The stability of reconstituted drugs varies from a few minutes (mecloethamine) to many months (FU). Compatibility data on two- and three-drug admixtures of cytotoxic agents are reported for a number of common multidrug regimens. Tabular presentation of the drug-drug compatibilities and incompatibilities is included along with a discussion of the mechanisms for drug-drug interaction. The use of a broad spectrum of compatible cytotoxic drugs is possible, including fluoropyrimidine-, anthracycline-, and platinum-based combinations, providing the capability of carrying out multidrug infusions for 4–7 days in an ambulatory delivery system.

Introduction

Parenteral antineoplastic drugs differ in their chemical stability. Some are more labile and rapidly degradable following reconstitution (e.g., mecloethamine), a few are sensitive to light (e.g., dacarbazine, doxorubicin, leucovorin, and methotrexate), and others are stable under a variety of conditions (e.g., cytarabine, cyclophosphamide, and fluorouracil). Treatment schedules involving continuous 24-h infusion of cytotoxic drug regimens in an ambulatory delivery system require that the drug be stable for days in a drug reservoir so as to provide optimal convenience to the patient.

When chemotherapeutic drug products are prepared for continuous-infusion therapy, they may be diluted with infusional diluents (e.g., dextrose for injection, sodium chloride for injection, sterile water for injection, and lactated Ringer's injection), stored under conditions beyond the control of the pharmacy or medical center, or admixed with other agents (drugs and/or excipients such as buffers or preservatives) in the product formulation. These conditions are deviations from the manufacturer's guidelines of quality assurance and may affect the stability of the drug, resulting in loss of activity, or result in the formation of a toxic product. Storage conditions are controllable provided that the patient is instructed to avoid exposing the infusion to strong sunlight, excessive heat, or freezing. Dilution with a vehicle that is not recommended by the manufacturer may affect the solubility of the drug or lead to alterations in chemical stability, i.e., by changing the pH of the final solution. Most diluents are thought to be inert in their capacity to react chemically with antineoplastic agents, yet dextrose is capable of reacting with antineoplastic drugs that possess a free amino group (e.g., bleomycin). The aldose form of dextrose can react with the free amino group to form a Schiff base, which can rearrange to form a stable product (the Maillard reaction).

When two or more drugs are admixed, the stability of one or all of the drugs may be compromised. The most common cause of incompatibility between drugs is a shift in the pH of the infusion formulation as a result of admixing. The consequence of a pH shift may be either a change in chemical stability or precipitation of one or more drugs. Admixing may also cause a direct reaction between two drugs, producing a new substance of unknown qualities, or a drug-adjuvant reaction that results in chemical incompatibility. Prediction of drug-vehicle, drug-drug, or drug-excipient incompatibilities requires that the nurse, pharmacist, and/or physician have knowledge of the factors that

Abbreviations: CBP, carboplatin; CDDP, cisplatin; CP, cyclophosphamide; DTC, decarbazine; DX, doxorubicin; D5W, dextrose for injection; FU, fluorouracil; FUDR, floxuridine; IF, ifosfamide; LV, leucovorin; MMC, mitomycin C; MTX, methotrexate; NS, sodium chloride for injection; R, Ringer's injection; SW, sterile water; VP16, etoposide

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affect the chemical and physical stability of the drugs they are handling.

Data on drug stability and compatibility as well as on factors affecting the storage of chemotherapeutic agents delivered as a bolus injection in which the drug is used soon after reconstitution are available in the package insert, in the *Handbook on Injectable Drugs* [52], in *NCI Investigational Drugs: Pharmaceutical Data* 1990 [51], and in *Chemical Stability of Pharmaceuticals: a Handbook for Pharmacists* [22]. However, there is a lack of information regarding the stability of multidrug admixtures over prolonged intervals, i.e., beyond that which is necessary for traditional bolus or short-term delivery of chemotherapy.

Multidrug admixtures represent a unique approach to combination chemotherapy. The compatibility of two or more antineoplastic agents is an important issue to be considered for multiple-agent infusions of drug admixtures. Another reason for knowing the stability and compatibility of antineoplastic drugs is the cost of these drugs and the relationship between wastage and improper preparation, which can increase cost and wastage.

This review represents a collation of reports in the literature from preclinical studies on the stability and compatibility of ad mixtures containing two or more antineoplastic agents. Our goal is to provide a resource relevant to the stability and compatibility of commonly used and investigational chemotherapeutic drugs delivered in single-agent (Table 1) or multidrug admixture infusions (Tables 2, 3).

Pharmaceutical principles

A practical program for continuous-infusion chemotherapy of protracted duration requires the establishment of the stability of individual antineoplastic agents at room temperature as well as their compatibility with the drug reservoir, polyvinylchloride (PVC) reservoir bags, or elastomeric infusion devices used for their delivery. Drug stability for a minimum of 5–7 days is most ideal for practical clinical management. Obvious evidence of antineoplastic instability or incompatibility can be observed as a color change, precipitation, or turbidity.

The most common physical change that lowers potency is precipitation of the antineoplastic drug. In some cases, degradation products may also precipitate. Crystallization results in an observable loss of drug in the final infusion. A drug is maintained in solution as long as its concentration remains below its saturation solubility, which is a function of temperature. Most water-insoluble drugs are less soluble at refrigerated temperatures than at room or body temperatures. When drugs that are poorly water-soluble are solubilized with a water-miscible cosolvent and diluted with an infusion fluid, a supersaturated solution may be produced and the drug may precipitate or crystallize at any time, especially if it is exposed to cooler temperatures. When diluted, cosolvents give a higher saturation level for the drug than does water alone (e.g., VP16). Another factor causing the antineoplastic drug to crystallize is the pH of the final infusion. Because most drugs are either weak acids or bases, their water solubility in the final solution is controlled by their respective ionization constants (p*Ka*), the final pH of the infusion, and the concentration of the nonionized drug at this pH. If the final pH of the infusion increases the amount of nonionized drug and this concentration exceeds the drug's maximal aqueous solubility, precipitation (or crystallization) is likely to occur. However, in some cases, the pH necessary to keep the drug in solution may also affect its chemical stability.

Stability is defined as the time during which a reconstituted antineoplastic drug retains its integrity in terms of quantity and chemical identity. The single drug or a multidrug admixture is considered to be stable when the drug concentration remains within acceptable limits, i.e., when the drug concentration(s) on any day of analysis is not less than 90% of its initial concentration. Compatibility as related to multidrug admixtures of antineoplastic agents defines the stability of the reconstituted admixture.

Once the chemotherapeutic drug has been reconstituted in an appropriate infusion fluid, the rate of drug degradation usually increases dramatically. Environmental factors such as temperature, pH, light, air, and the type of container used can affect the stability of the final solution. The single most important factor affecting drug stability is pH, which can have a dramatic effect on the stability of labile drugs [58]. It is possible to predict drug-infusion fluid or drug-drug incompatibilities due to changes in pH, provided that the pH range for optimal stability of the chemotherapeutic drug is known [45]. In most cases, the incompatibility or instability of a drug in an infusion is due to pH shifts, not to drug-drug interactions. Caution is required during dilution of the reconstituted solution with SW, D5W, and NS. Because most single-agent formulations used in making an admixture are unbuffered, the final pH of an admixture of two or more different drugs is determined by the solution in largest volume or concentration.

The second most important factor that can influence the rate of degradation and substance stability is temperature. An increase of 10°C in the storage temperature can enhance chemical degradation by a factor of 2–5. This becomes especially important if the infusion pump and drug reservoir are carried under clothing next to the body.

The loss of antineoplastic potency due to chemical degradation in infusion fluids usually results from hydrolysis, oxidation, or photolysis. Hydrolysis is the most frequently encountered type of chemical reaction responsible for drug degradation in aqueous solutions and is usually pH-dependent [22]. Control of the pH can optimize the stability of the infusion. Oxidation reactions proceed through a mechanism involving oxygen and can be catalyzed by light, pH, and metal ions. Some of the antineoplastic drugs most susceptible to oxidation include doxorubicin, dacarbazine, methotrexate, and leucovorin. Oxidation reactions in infusion solutions can be controlled by pH and protection from light. The degassing of infusions in plastic bags to exclude air is not very practical because of the diffusibility of air through the bag. Photolysis describes the light-catalyzed degradation of substances, which is dependent not only on the wavelength of the light but also on its intensity and on the pH of the solution. Ultraviolet light is more deleterious than visible light to photolabile drugs and encompasses the range from 180 to 380 nm, with sunlight falling in the 290- to 380-nm range and fluorescent light, between 320 and

Table 1. Stability of individual reconstituted antineoplastic agents

Drug	Reconstituted concentration	Infusion fluid	Stability[a, b]	References
Alkaloids and glycosides:				
Vinblastine	1 mg/ml	NS,DW,R	21 days @ 25° C	[14, 53]
Vincristine	1 mg/ml	NS,DW,R	21 days @ 25° C	[14, 54]
Etoposide	20 mg/ml	NS,DW,SW	5–28 days @ RT	[1, 15, 27]
Alkylating agents:				
Carmustine	3.3 mg/ml	NS,DW	8 h @ RT	PI
Cyclophosphamide	20 mg/ml	DW,NS,SW	4–6 days @ RT	[19]
Dacarbazine	10 mg/ml	NS[c]	24 h @ 20° C	Williams, unpublished data
		NS	8 h @ 35° C	Williams, unpublished data
Ifosfamide	50 mg/ml	DW,NS,R	7 days @ RT	[50]
		NS	9 days @ 37° C	[39]
Mecloethamine	1 mg/ml	NS	Use immediately	PI
Thiotepa	10 mg/ml	NS,DW,SW,R	5 days @ 5° C	PI
Antibiotics:				
Bleomycin	3 units/ml	NS	24 h @ RT	[31]
		DW	8 h @ RT	[31]
Daunorubicin	5 mg/ml	DW,NS,R	80–108 h @ 21°–25° C	[7,8, 38]
		R	54 h @ 21° C	[9]
Doxorubicin	2 mg/ml	DW	4–28 days @ 21°–25° C	[7 ,8, 38]
		NS	100 h @ 25° C	[7, 8, 38]
		NS	63 h @ 21° C	[7, 8, 38]
		R	28 h @ 21° C	[7, 38]
Mitomycin C	0.5 mg/ml	DW	Unstable @ RT	[10, 12]
		SW	7 days @ 25° C	Bristol-Myers, unpublished data
		NS,DW,R	6–48 h @ RT	Bristol-Myers, unpublished data
Mitoxanthrone	2 mg/ml	NS,DW,SW	7 days @ 25° C	[13]
		NS	28 days @ 20° C	[1]
Pentostatin	2 mg/ml	NS,R	2–3 days @ RT	[51]
		DW	1 day @ RT	[51]
Antimetabolites:				
Cytarabine	20–25 mg/ml	DW,NS,SW,R	14 days @ RT	[52]
Floxuridine	100 mg/ml	DW,NS,SW	14 days @ RT	[3, 52]
Fludarabine Phos.	25 mg/ml	DW,NS,SW	16 days @ RT	[51]
Fluorouracil	50 mg/ml	DW,NS,SW	14–42 days @ RT	[5, 52, 55]
Methotrexate	1–50 mg/ml	DW[c]	7–42 days @ RT	[25, 29, 55]
Leucovorin	5–10 mg/ml	NS,DW[c]	7 days @ RT	[37]
Metal complexes:				
Cisplatin	1 mg/ml	NS[c]	14 days @ RT	[1, 35]
Carboplatin	10 mg/ml	SW	1–7 days @ RT or 4° C	[21, 43]; Williams, unpublished data
		NS	24–48 h @ RT	[21, 43]; Williams, unpublished data

[a] Stable within the specified period (<10% degradation)
[b] RT is the room-temperature range from 20° to 25° C
[c] Protected from light
RT, room temperature; PI, Manufacturers package insert

380 nm. Photolabile antineoplastic drugs include the anthracycline antibiotics, dacarbazine, methotrexate, leucovorin, and the platinum complexes. Finally, drug-drug chemical incompatibility relates to a chemical reaction between two chemotherapeutic drugs or between the chemotherapeutic drug and the infusion additives, resulting in the formation of a new compound or degradation product that may be more or less biologically active than the original agent(s).

Stability and compatibility

The chemical stability data reported in Table 1 for individual antineoplastic agents generally indicates a shelf life for the reconstituted drug that ranges from a few hours to 28 days. Those that remain stable for less than 24 h require the daily administration of freshly prepared solutions. Once a drug has been reconstituted or diluted or is in use, manufacturers recommend that the solution be discarded within 8–24 h. This does not necessarily imply that drug degradation occurs immediately beyond that period; rather, this recommendation may be related to maintaining the sterility of the final solution. Antineoplastic drugs in single-use vials do not usually contain antimicrobial preservatives. Therefore, during the preparation of admixtures from these vials, aseptic techniques are observed; otherwise, significant microbial contamination could result within 24 h. Dilution of the reconstituted drug solution with bacteriostatic diluents (preserved with either benzyl alcohol or parabens) is recommended for most antineoplastic drugs so as to maintain sterility for 6–7 days, the excep-

Table 2. Drug stability for admixtures containing two antineoplastic agents

Drugs		Infusion fluid[a, b]	Stability	References
Fluorouracil (10 mg/ml)	+ cyclophosphamide (1 mg/ml)	NS	14 days @ RT	[34]
Fluorouracil (10 mg/ml)	+ floxuridine (10 mg/ml)	NS	15 days @ RT	[4]
Fluorouracil (10 mg/ml)	+ etoposide (0.2 mg/ml)	NS	7 days @ RT	Williams, unpublished data
Fluorouracil (10 mg/ml)	+ etoposide (0.2 mg/ml)	NS	1 day @ 35° C	Williams, unpublished data
Fluorouracil (10 mg/ml)	+ methotrexate (0.025 mg/ml)	NS[c]	15–42 days @ RT	[34, 55]
Fluorouracil (10 mg/ml)	+ leucovorin (0.2 mg/ml)	NS	15 days @ RT	[3]
Fluorouracil (50 mg/ml)	+ epirubicin (1 mg)	NS	Unstable @ 25° C	[1]
Fluorouracil (10 mg/ml)	+ carboplatin (1 mg/ml)	SW	Unstable @ RT	Williams, unpublished data
Cisplatin (0.2 mg/ml)	+ etoposide (0.2–0.4 mg/ml)	NS[c]	7–14 days @ RT	[33]
Cisplatin (0.2 mg/ml)	+ etoposide (0.2–0.4 mg/ml)	NS[c]	48 h @ RT	[46]
Cisplatin (0.2–0.5 mg/ml)	+ fluorouracil (1–10 mg)	NS[c]	3–24 h @ RT	[32, 47]
Cisplatin (1 mg)	+ floxuridine (10 mg)	NS[c]	7 days @ RT	[32]
Cisplatin (0.2 mg/ml)	+ leucovorin (0.2 mg/ml)	NS[c]	15 days @ RT	Williams, unpublished data
Cisplatin (0.2 mg/ml)	+ MESNA (1 mg)	NS[c]	Unstable @ RT	Williams, unpublished data
Cisplatin (0.2 mg/ml)	+ thiotepa (1 mg/ml)	NS[c]	Unstable @ RT	Williams, unpublished data
Cisplatin (0.2 mg/ml)	+ carboplatin (1 mg/ml)	NS[c]	24 h RT	Williams, unpublished data
Floxuridine (10 mg/ml)	+ leucovorin (0.2 mg/ml)	NS	14 days @ RT	[3]
Floxuridine (1.2, 4 mg/ml)	+ leucovorin (0.2 mg/ml)	NS	48 h @ RT	[44]
Floxuridine (10 mg/ml)	+ etoposide (0.2 mg/ml)	NS	15 days @ RT	Williams, unpublished data
Methotrexate (0.025 mg/ml)	+ cyclophosphamide (1.66 mg/ml)	NS[c]	7 days @ RT	[34]
Ifosfamide (50 mg/ml)	+ MESNA (80 mg/ml)	NS	28 days @ 20° C	[1]
		NS	9 days @ 37° C	[39]
Ifosfamide (50 mg/ml)	+ epirubicin (0.5 mg/ml)	NS	28 days @ 20° C	[1]
Ifosfamide (2 mg/ml)	+ cisplatin (0.2 mg/ml)	NS[c]	7 days @ RT	Williams, unpublished data
Ifosfamide (2 mg/ml)	+ fluorouracil (10 mg/ml)	NS	5 days @ RT	Williams, unpublished data
Ifosfamide (2 mg/ml)	+ etoposide (0.2 mg/ml)	NS	7 days @ RT	Williams, unpublished data
Ifosfamide (2 mg/ml)	+ carboplatin (1 mg/ml)	SW	5 days @ RT	Williams, unpublished data
Doxorubicin (1 mg/ml)	+ fluorouracil (50 mg/ml)	NS	Unstable @ RT	[1]; Williams, unpublished data
Doxorubicin (1.4 mg/ml)	+ vincristine (0.033 mg/ml)	NS,DW	7 days @ 37° C	[11]
Carboplatin (1 mg/ml)	+ sodium bicarbonate (200 mM)	SW	Unstable @ RT	Williams, unpublished data
Carboplatin (1 mg/ml)	+ floxuridine (10 mg/ml)	SW	7 days @ RT	Williams, unpublished data
Carboplatin (1 mg/ml)	+ etoposide (0.2 mg/ml)	SW	7 days @ RT	Williams, unpublished data
Carboplatin (1 mg/ml)	+ MESNA (1 mg/ml)	SW	Unstable @ RT	Williams, unpublished data

[a] Stable/compatible within the specified period (<10% degradation)
[b] RT is the room-temperature range from 20° to 25° C
[c] Protected from light
RT, Room temperature

tions being DX and CP (preserved with paraben only). If this reconstituted solution or admixture is improperly prepared or is not used, it is wasted, which adds to the patient's cost. The conditions of reconstitution generally conform to the manufacturer's recommendations, with the solution being maintained at room temperature. The stability of individual and multiple agents that have been appropriately reconstituted and formulated for patient delivery have recently been reviewed [58] and are summarized in Tables 1–3.

Each of the antineoplastic compounds is evaluated as a single agent and as admixed with other agents on the basis of planned clinical trials. The subsequent sections of this review are separated into individual classes of drugs within which single-drug stability and two- and three-drug compatibility studies have been conducted.

Antibiotics

The anthracycline antibiotics (doxorubicin and daunorubicin) represent a major class of antineoplastic agents that exhibit a broad spectrum of anticancer activity. Although mitoxantrone is not an antibiotic, it is similar to the anthracyclines in its stability properties. Bleomycin is a group of antineoplastic glycoproteins, and mitomycin C is an aziridinoquinone antibiotic activated in vivo to a bifunctional alkylating agent.

The anthracycline antibiotics are tetrahydronaphthacenequinone aminoglycosides whose stability in aqueous solutions are greatly influenced by light, infusion concentration, the pH of the infusion admixture, dissolved oxygen, and temperature [7, 8]. Due to the optimal pH range of 3–6.5 for DX, a neutral-alkaline pH increases the rate of degradation for DX infusions and should be avoided. Generally, under these conditions, chemical incompatibility is readily observable as the formation of a precipitate or a change in color from red-orange to blue-violet.

DX is incompatible with solutions containing fluorouracil ([1]; Williams, unpublished data), dexamethasone sodium phosphate [52], and sodium bicarbonate [52] but forms complexes with many metals that catalyze its degradation [18, 52]. It adsorbs to the surface of glass, Teflon (PTFE), and polyethylene containers but not to polypropy-

Table 3. Drug stability for admixtures containing three antineoplastic agents

Drugs	Infusion fluid	Stability[a, b]	References
Cisplatin (0.2 mg/ml) Etoposide (0.2 mg/ml) Ifosfamide (2.0 mg/ml)	NS[c]	5 days @ RT	Williams, unpublished data
Carboplatin (1.0 mg/ml) Etoposide (0.2 mg/ml) Ifosfamide (2.0 mg/ml)	SW	7 days @ RT	Williams, unpublished data
Cisplatin (0.2 mg/ml) Etoposide (0.2 mg/ml) Cyclophosphamide (2.0 mg/ml)	NS[c]	7 days @ RT	Williams, unpublished data
Daunorubicin (0.033 mg/ml) Etoposide (0.4 mg/ml) Cytarabine (0.27 mg/ml)	NS,DW	72 h @ 20° C	[42]
Fluorouracil (5.0 mg/ml) Floxuridine (0.7 mg/ml) Leucovorin (0.14 mg/ml)	NS[c]	15 days @ RT	[3]
Cyclophosphamide (2.0 mg/ml) Fluorouracil (10.0 mg/ml) Methotrexate (0.03 mg/ml)	NS[c]	15 days @ RT	[34]
Cisplatin (0.2 mg/ml) Floxuridine (0.7 mg/ml) Leucovorin (0.14 mg/ml)	NS[c]	7 days @ RT	Williams, unpublished data
Cisplatin (0.2 mg/ml) Floxuridine (0.7 mg/ml) Etoposide (0.3 mg/ml)	NS[c]	7 days @ RT	Williams, unpublished data
Fluorouracil (5 mg/ml) Methotrexate (0.01 mg/ml) Leucovorin (0.1 mg/ml)	NS[c]	7 days @ RT	Williams, unpublished data
Ifosfamide (50 mg/ml) MESNA (80 mg/ml) Epirubicin (0.5 mg/ml)	NS	Unstable @ 25° C	[1]

[a] Stable/compatible within the specified time period (<10% degradation)

[b] RT is the room temperature range from 20° to 25° C

[c] Protected from light

lene surfaces [49]. It has been recommended that reconstituted DX not be diluted with bacteriostatic sterile water or NS containing benzyl alcohol [52]. When stored in D5W at room temperature and protected from light, infusions of DX (0.02–0.1 mg/ml) remain stable for 3–28 days; when stored in NS, their stability is 6 days [7, 16, 38]. Its increased stability in D5W can be attributed to the acidic pH of the latter. The observation that DX is more stable in PVC bags has been attributed to the selected filtering of light by these bags [48]. These studies demonstrate not only that pH is important in the selection of the infusion fluid but also that the combined effect of light and pH on the stability of the anthracycline antitumor agents should be considered.

The stability of an admixture of DX (1.4 mg/ml) and vincristine (0.033 mg/ml) in NS, D5W, and Ringer's acetate is dependent on the infusion solution [11]. Both vincristine and DX were stable at 37° C for 7 days in NS or 0.45% NS-2.5% DW. However, in 0.45% NS-Ringer's acetate injection (pH 8), the concentration of DX fell to less than 90% of the original level within 24 h at 25° C and vincristine remained stable for 7 days at 25° C and for 2 days at 37° C; a color change was observable that was indicative of DX degradation.

Daunorubicin, a structural analog of DX, is more stable than DX over a wider pH range (pH 4–7) [7, 9]. The stability of its solutions are pH-dependent, with degradation occurring more readily at pH <4 and >8 (color change from red to blue). Infusions of daunorubicin should also be protected from light. Idarubicin, a new anthracycline that is structurally related to daunorubicin, has physicochemical properties similar to those of daunorubicin. Therefore, during the preparation of infusions of idarubicin, the same precautions for preserving the stability of DX and daunorubicin infusions should be followed [52].

Because of the higher concentrations of DX used in cancer chemotherapy, the more deeply colored solution protects DX from photolytic decomposition [48]. Therefore, no special precaution is needed to protect the solution from light for 24 h, but infusions given over an extended period should be protected from both sunlight and room light to ensure stability and adequate drug concentration.

The many discrepancies in the literature regarding the stability of anthracyclines in infusion fluids are likely related to differences in the concentrations studied, to the use of unbuffered solutions, to the lack of pH control or the failure to protect the infusions from photodegradation, or to metal complexation.

When epirubicin is reconstituted (1 or 2 mg/ml) in NS or D5W in plastic syringes or glass vials, no significant degradation occurs over 150 days at 4° or 23° C [56].

The dark-blue reconstituted solution of mitoxantrone HCl (pH 4) in D5W or NS (0.2–0.5 mg/ml), a synthetic anthraquinone analog of the anthracycline antibiotics, is stable for 1 week at room temperature and after 1 month of sunlight exposure [13, 51]. Its optimal pH range is 2–4.5 [13]. However, aqueous solutions of mitoxantrone have been found to be unstable at room temperature when the pH is >7 [40, 57]. Mitoxantrone HCl (2 mg/ml) reconstituted in NS or D5W in glass vials and plastic syringes show's no significant loss in potency after 42 days at 4° or 23° C [57].

Bleomycin sulfate is stable over a pH range of 4–10, and the pH of its reconstituted solution is 4.5–6. It has previously been reported [17, 24] that when bleomycin is reconstituted in D5W, a rapid loss of drug occurs within a few hours of storage in PVC bags but not in glass containers. However, on the basis of a recent study investigating the loss of bleomycin reconstituted in D5W (3 units/ml) in either PVC or glass containers, this loss can be attributed to the formation of a Schiff-base reaction product (Maillard reaction) between dextrose and the amino groups of bleomycin [31]. Furthermore, no significant loss of bleomycin occurred when the drug was reconstituted in NS, whether in PVC or glass containers.

The cytotoxicity of mitomycin C occurs only after enzymatic and/or acid activation to a bifunctional alkylating agent that cross-links DNA through the "activated" aziridine ring [20]. Therefore, it is not surprising that its reconstitution and/or dilution with an acidic infusion vehicle or its admixture with other acidic chemotherapeutic infusions can cause rapid degradation of MMC by acid-catalyzed hydrolysis (ring opening) of the aziridine ring [10, 12]. Its maximal stability occurs at neutral pH and is influenced by temperature and buffer concentration. At a pH higher or lower than 7, the rate of degradation increases proportionally to the concentration of H^+ or OH^- in the final infusion.

The stability of reconstituted MMC is as follows: in SW (0.5 mg/ml), 7 days at room temperature and 14 days at 4° C; in NS (0.02–0.04 mg/ml), 12–24 h at 25° C and 14 days at 4° C; in DSW (0.02–0.04 mg/ml), 6–24 h at 25° C; and in lactated Ringer's 24 h at 25° C [12]. However, its dilution to 0.05 mg/ml in D5W or NS results in significant losses of MMC within 12–24 h at 4° C or room temperature, with greater losses occurring in D5W [12, 16]. Its decreased stability in D5W may be due to the acidic pH of the diluent. Dexamethasone sodium phosphate and hydrocortisone sodium succinate are reportedly compatible with MMC (0.01 and 0.1 mg/ml) for at least 24 h when stored at room temperature or 4° C in glass or PVC containers (Bristol-Myers, Oncology Division, unpublished data). An admixture (initial pH, 7.5) of fluorouracil (2 mg/ml) and MMC (0.02 mg/ml) has remained stable for only 24 h in glass or PVC bags at room temperature (Williams, unpublished data). Studies dealing with the stability of MMC in infusion fluid are unanimous in demonstrating that the pH of the solution is the critical parameter and should be neutral. The discrepancies in the literature regarding the stability of MMC in infusion fluids are likely related to the lack of pH control.

Pentostatin (2′deoxycoformycin) reconstituted in NS (2 mg/ml) is chemically stable for 72 h at room temperature [51]. When diluted to 0.02 mg/ml in NS or lactated Ringer's injection, it remained stable for 48 h at room temperature, but the loss was 8%–10% under the same conditions in D5W. At 5° C in D5W or NS, no significant loss of pentstatin occurred within 96 h. Its optimal pH for stability appears to be in the range of 7–8.

Plant alkaloids and glycosides

The anticancer plant alkaloids include vinblastine, vincristine, and vindesine, which are derived from the *Vinca* (periwinkle) plant. Etoposide is a semisynthetic glycoside derived from podophyllotoxin. Vinblastine and vincristine display significant differences in chemical stability in aqueous solution. Vinblastine is more stable in the pH range of 2–4, and vincristine is more stable at pH 4–6 [53, 54]. The principal route of degradation for both drugs is pH-dependent hydrolysis to the respective inactive desacetyl derivatives. Therefore, the preparation of admixtures of the vinca alkaloids with alkaline antineoplastic drugs for continuous infusion is not recommended when the resultant pH is >7. Photodegradation does not appear to be a significant problem with the vinca alkaloids. Vinblastine (0.02 mg/ml) and vincristine (0.02 mg/ml) in the infusion fluids D5W, NS, and lactated Ringer's exhibited less than a 5% loss over 3 weeks when stored at 4° and 25° C [14]. However, the basis for a 24% loss of vinblastine (1 mg/ml NS) within 24 h at 37° C when the solution was placed in an implantable device could not be ascertained because of the different materials comprising the device [30]. Vinblastine (0.04 mg/ml), vincristine (0.008 mg/ml), and vindesine (0.016 mg/ml) reconstituted in D5W or NS remain stable for 7 days at 4° C in PVC bags [23]. The stability of an admixture of doxorubicin and vincristine has been described elsewhere [11].

VP16 is poorly soluble in water and is therefore supplied as a solution in polyethylene glycol-ethanol. The principal problem with VP16 is the physical instability caused by precipitation when the special vehicle is diluted with aqueous infusion fluids. The onset of crystallization depends on the final drug concentration, and crystals can appear after several hours or days at a VP16 concentration of 0.4 mg/ml, depending on the storage temperature. At a concentration of 0.2 mg/ml, precipitation is less likely to occur, whereas crystals appear readily at 1 mg/ml. The refrigeration of diluted solutions often causes precipitation, and heating to redissolve the crystals may compromise the stability of VP16 and any other drug that may be present. The optimal pH range for VP16 stability is 4–6. At a pH of <4, hydrolysis of the glycosidic linkage and the lactone ring occurs, and at a pH of >6, epimerization to the less active *cis*-VP16 and intramolecular ester hydrolysis into the salt of the *cis* hydroxy acid ensues [15, 27]. Otherwise, VP16 structurally does not appear to pose any significant incompatibility with other antineoplastic drugs. Data on

the stability and compatibility of VP16 with other antitumor drugs are presented in Tables 2 and 3.

Alkylating agents

The major alkylating agents that are given parenterally and are stable on reconstitution include cyclophosphamide, ifosfamide, and thiotepa. The other classic and nonclassic alkylating agents, including the nitrogen mustards (mechloethamine) and the triazenes (dacarbazine), are generally less stable. As this class of agents has undergone limited clinical trials using infusion schedules, minimal data are available on their stability and compatibility.

Nitrogen mustards exert their antitumor activity through the reactivity of the chloroethyl "mustard arm." When dissolved in water or diluted with aqueous infusion fluids, the nitrogen "mustard arm" undergoes pH-controlled hydrolytic displacement of the chloro group(s). Degradation in aqueous solution may be stabilized by the addition of excess chloride ion, which retards or, in some cases, reverses the hydrolysis by its common ion effect. However, the presence of other anions or nucleophiles (e.g., buffers, mercaptans, and bisulfite) or the presence of other drugs may diminish the stabilizing effect of the chloride ion concentration. The effect these drugs or adjuvants have on the stability of the mustards cannot be accurately predicted.

The tumor-alkylating properties of CP are due to the phosphoramide mustard, which is derived from the hydrolysis of its hepatic metabolite, 4-hydroxycyclophosphamide. Solutions of CP (21 mg/ml) remain stable for at least 4–6 days in D5W, NS, lactated Ringer's and other infusional diluents [19]. The greater stability of CP under conditions of hydrolysis is attributable to the phosphoramide group, which prevents the rapid formation of its alkylating intermediate, the ethyleneimmonium ion.

In light of the known stability of CP and its potential for continuous-infusion therapy, the stability of CP alone and in admixtures has been reported [34]. CP admixtures in NS remain stable for at least 7 days in PVC bags at room temperature. It is recommended that CP be diluted *not* with bacteriostatic SW or NS preserved with benzyl alcohol but rather with bacteriostatic SW or NS preserved with parabens. However, the CP (1.66 mg/ml)-MTX (0.025 mg/ml) combination shows a 6.6% loss of CP after 14 days at room temperature and a drop in pH from 6.3 to 4.57. The incompatibility does not appear to be due to hydrolysis of CP, as an FU-CP mixture (pH 8.4) was stable for 14 days at room temperature, and only after 24 h storage at pH 10 and 35° C was significant degradation (>10%) of CP observed (Williams, unpublished data). There was no significant change in the concentration of MTX, indicating the lack of a drug-drug interaction. A triple combination of CP (1.66 mg/ml), MTX (0.025 mg/ml), and FU (8.3 mg/ml; pH 8.23) remained stable for 7 days in PVC bags protected from light at room temperature [34], although a 9.3% loss of CP was noted at 14 days.

IF, an analog of CP, is likewise activated by liver microsomes and converted into its phosphoramide alkylating analog. IF (16 and 0.6 mg/ml) remains stable for at least 7 days in D5W, NS, lactated Ringer's, and other infusional diluents [50]. In aqueous solution, IF alone or mixed with mesna is stable for at least 9 days at 27° and 37° C, although a greater loss (7%) has been observed at 37° C [39]. However, when IF (100 mg/ml) was reconstituted in SW preserved with 0.9% benzyl alcohol, a turbid solution (indicative of a physical incompatibility) resulted, but this turbidity did not occur at a concentration of 60 mg/ml [6]. The stability and compatibility of IF (2 mg/ml) with CDDP (0.2 mg/ml) in NS, with VP16 (0.2 mg/ml) in NS, with CBP (1 mg/ml) in SW, or with FU (10 mg/ml) in NS, as well as triple combinations of the fluoropyrimidine with CDDP and VP16 in NS and with CBP and VP16 in SW have been investigated in our laboratory (Williams, unpublished data). Each of the admixtures examined was stable for 7 days, except for the IF-CBP, IF-FU, and IF-CDDP-VP16 infusions, which remained stable for 5 days. The studies were terminated when the IF concentrations fell below 90%, even though the other antineoplastics remained stable. IF (50 mg/ml), mesna (80 mg/ml), and epirubicin (0.5 mg/ml) were incompatible [1]. A 50% loss of epirubicin was observed after 7 days at room or refrigerator temperatures [1]. This was attributed to a mesna-epirubicin interaction because mesna-IF and epirubicin-IF combinations remained stable for 14 days under similar conditions. Because mesna is frequently used in combination with IF, the effect of adding mesna to CDDP and to CBP solutions was also examined (Williams, unpublished data). Mesna was incompatible with CDDP and CBP, resulting in a rapid degradation of the platinum complexes within 24 h at room temperature.

Thiotepa, an ethyleneimminephosphoramide, acts as an alkylating agent similar to the mustards. Because acidic conditions catalyze its hydrolysis, reconstituted solutions of thiotepa are stabilized with sodium bicarbonate (50 mg/vial). In a single experiment carried out to test the compatibility of a thiotepa-CDDP admixture, a solution of thiotepa (1 mg/ml) with CDDP (0.2 mg/ml) in NS was prepared, but a yellow precipitate formed within 24 h (Williams, unpublished data). High-performance liquid chromatographic (HPLC) analysis showed a 20% loss of CDDP, but no analysis for thiotepa was conducted. The observed incompatibility of the thiotepa-CDDP admixture and resultant loss of CDDP is attributed to a chemical reaction between CDDP and sodium bicarbonate [41].

Preliminary studies carried out in our laboratory to investigate the suitability of DTIC for continuous-infusion chemotherapy confirmed not only that it is very photosensitive [28] but also that temperature affects its stability. The results of our experiments clearly show that DTIC solutions exposed to direct and indirect sunlight rapidly degrade within 3–4 h (Williams, unpublished data). The maximal stability of DTIC under exposure to fluorescent light at room temperature was 24 h (Williams, unpublished data). Temperature greatly influences the stability of DTIC in solution. When protected from light, DTIC solutions remain stable (<10% loss) for up to 48 h at 20° C, for 24 h at 25° C, and for 8 h at 35° C. A color change from a nearly colorless state to an intense pink or maroon color indicates that decomposition of DTIC has occurred.

Antimetabolites

The antimetabolites used clinically as infusions include the fluoropyrimidines FUDR and FU, the antifolate MTX, and cytarabine. Leucovorin calcium (LV) is also included because of its structural and chemical similarity to MTX. In general, the fluoropyrimidine and cytarabine antimetabolites demonstrate greater stability over a wide range of conditions. MTX and LV are photolabile, and the thiopurines are hydrolyzed.

Aqueous solutions of MTX are most affected by sunlight, normal room lighting, and extremes of pH [26]. The storage of MTX in D5W unprotected from normal room lighting at room temperature results in a 6.21% and 14.9% loss of MTX concentration after 72 h and 1 week, respectively [29], but under protection from light, the loss after 1 week is 6.1%. PVC bags have been shown to protect MTX in solution against photochemical degradation on its exposure to room light. This protection has been attributed to the filtering of select wavelengths of light by PVC [25]. It has been recommended by a number of sources that infusions containing MTX should be protected during preparation and storage from direct sunlight and room light [36]. The optimal pH range for the stability of MTX is 6.6–8.2; thus, pH values of <5 and >9 accelerate its rate of degradation. An isotonic solution of MTX (0.03 mg/ml) stored in NS at pH 8.2 and 25° C under protection from light has een estimated to remain stable for 54 months [26].

FU is solubilized as its sodium salt to give a solution with a pH of 8.5–9. This solution remains stable for many months under normal conditions [5, 52]. If the pH falls below 8, FU may or may not precipitate, depending on its final concentration in the infusion and on how far this concentration lies below its saturation solubility. Because the FU concentration in commercial solution (50 mg/ml) is at or near its saturation solubility, precipitation of FU can occur on refrigeration. The high alkalinity of FU injection affects the stability of substances whose degradation is catalyzed in an alkaline media, e.g., by hydrolysis or oxidation. Esters, lactones, platinum complexes, and phenols are a few of the substances that, if present in an admixture with FU, are subject to alkaline hydrolysis and/or oxidation. Thus, when preparing admixtures containing FU, one must evaluate not only the type of substance involved but also the effect of pH and temperature so as to predict whether the final infusion admixture will be stable and compatible in an alkaline media. To determine further the effect of the alkalinity of FU infusion on its stability and compatibility with other antineoplastic drugs, our laboratory has examined the compatibility of FU-CDDP, FU-VP16, and FU-CBP admixtures (Williams, unpublished data). The combination of FU (1–10 mg/ml) and CDDP (0.2–0.5 mg/ml) in NS was unstable, resulting in an 80% loss of CDDP within 24 h [32], with most of the loss occurring within 2–3 h [47]. In an investigation of the possibility that the alkalinity of the FU injection in an admixture with VP16 might catalyze the hydrolysis and epimerization of VP16, an FU-VP16 admixture was found to be stable for at least 7 days at room temperature, and a 36% loss of VP16 was observed within 2 days at 35° C (Williams, unpublished data). Furthermore, an FU-CBP admixture exhibited incompatibility (an 8% and a 20% CBP loss within 12 and 24 h, respectively) at room temperature (Williams, unpublished data). A precipitate formed rapidly when FU (50 mg/ml) was admixed with epirubicin (1 mg/ml) or with DX (0.5–1 mg/ml) [1].

Floxuridine is a pyrimidine nucleoside that is water-soluble and stable under neutral or mildly acid/alkaline conditions, and its optimal pH for stability is 4–7. Previous studies in our laboratories showed that no significant degradation occurred when admixtures of FUDR (10 mg/ml) with FU (10 mg/ml) [4], with LV (0.2 mg/ml) and FU (10 mg/ml), or with LV (0.2 mg/ml) [3] in NS were stored at room temperature in PVC bags protected from light over a 14-day period. However, an FUDR-LV admixture (pH 5.2) stored at 40° C exhibited an 11.6% loss of LV in 15 days, whereas no change occurred in the FU-LV solution (pH 8.7) [3]. Admixtures of LV (30, 240, and 960 μg/ml) with FUDR (1.2 and 4 mg/ml) in NS remained stable for 48 h at 20° C but exhibited degradation at 40° C [44].

Reconstituted aqueous solutions of LV are subject to photodegradation and hydrolysis, and infusion solutions should therefore be protected from light. The solutions are most stable at a pH of >7, as hydrolysis occurs in acidic media (pH <5) [37]. Information supplied by the manufacturer report that the reconstituted solution (pH 6–8) remains stable for about 7 days when protected from light.

Cytarabine (cytosine arabinoside) is very stable at pH 5–8 and its stability is independent of the pH and the type of infusion fluid used [52]. It has been estimated that cytarabine remains stable for up to 6 months at pH 6.9 and 25° C. At 37° C, no significant loss of cytarabine (1.2 mg/ml) occurs within 15 days in an implantable pump device.

Fludarabine phosphate (2-fluoroadenine arabinoside-5′-monophosphate) reconstituted in SW (25 mg/ml) exhibits less than a 2% loss within 16 days [51]. It remains relatively stable over a pH range of 4.5–8 and exhibits less than a 10% loss over 3 days at 65° C, but at pH 3 it is unstable, showing an 11% loss. Its optimal pH is approximately 7.6. When diluted for infusion to 1 mg/ml in D5W or NS, fludarabine phosphate remains stable (less than 3% loss) for 16 days [51] at room temperature. When it is stored at 0.04 mg/ml in D5W or NS in PVC bags or glass bottles, no significant loss occurs within 48 h at room temperature.

Metal complexes

The only metal complexes used clinically as antineoplastic drugs are cisplatin and carboplatin, although iproplatin and tetraplatin are currently under investigation for clinical application.

Hydrolytic displacement reactions and photosensitivity represent the most important degradation mechanisms for CDDP [35, 41]. Dissolution of CDDP in SW or D5W in the absence of sodium chloride results in the formation of a hydrated platinumammine complex because of aquation (hydrolytic displacement of the chloro groups), causing a significant loss of CDDP within 24 h. However, its stabil-

ity can be optimized by dissolution in 0.45% NS or NS, yielding an optimal pH range of 3.5–5.5. A yellow precipitate of CDDP may be observed as a sign of physical instability because of its poor water solubility (2.5 mg/ml in water or 1 mg/ml in NS). Infusions demonstrating a precipitate should be discarded. Attempts to redissolve the CDDP by heating can affect its stability as well as that of other drugs present.

Of particular importance is the compatibility of co-delivered drugs and other adjuvants with CDDP. The addition of CDDP to 5% sodium bicarbonate (pH 7.5) resulted in the formation of a yellow precipitate on standing, indicating that decomposition of the CDDP had occurred [41]. A loss of CDDP was observed after 5 days when an infusion of FUDR (10 mg/ml) and CDDP (1 mg/ml) was stored in a PVC bag at room temperature [32]. An alkaline media increases the rate of its hydrolysis and should be avoided in the preparation of CDDP admixtures. The presence of sodium bisulfite or metabisulfite, an antioxidant for easily oxidized drugs, also causes the decomposition of CDDP, resulting in the formation of a precipitate [41].

Previous studies using an admixture of VP16 (0.4 mg/ml) and CDDP (0.2 mg/ml) demonstrated no significant loss of either drug within 7 days at room temperature when the infusion mixture was protected from light; however, after 7 days a 10% loss of VP16 was observed due to its precipitation [33]. Decreasing the concentration of VP16 in the VP16/CDDP admixture from 0.4 to 0.2 mg/ml resulted in no precipitation of VP16 and increased the stability to 14 days. Stewart and Hampton [46] showed that an admixture of CDDP (0.2 mg/ml) and VP16 (0.2 and 0.4 mg/ml) in NS or NS/D5W was stable for about 48 h at room temperature when protected from light, but the presence of mannitol or potassium chloride in the admixture caused precipitation of VP16 to occur. However, when the solutions were not protected from fluorescent room light, a 5%–10% loss of CDDP resulted within the 48-h study period, depending on the infusion fluid used.

The optimal stability for CBP infusions is achieved by dissolution of the drug in D5W or SW, but NS limits its stability to 24 h at 25° or 37° C [2, 21, 43]. The chloride ion apparently converts CBP to CDDP [21]. This incompatibility is of little significance in single-agent infusions because the use of chloride-containing infusion fluids can be avoided [43]. However, in multiple-agent therapy it may be necessary to prepare admixtures of CBP with other antineoplastic drugs in which chloride ions are present. We extended this study to investigate the stability of CBP in SW as well as admixtures of the drug with FUDR, FU, and CDDP (Williams, unpublished data). During storage at 27°C in NS, 92% of the initial CBP concentration (1 mg/ml) persisted after 48 h (Williams, unpublished data). When stored at 4° and 27°C in SW, CBP retained 96%–100% of its concentration for 5 and 7 days, respectively ([2, 43]; Williams, unpublished data). A CBP (1 mg/ml)-FUDR (10 mg/ml) infusion solution remained stable for 7 days; however, CBP (1 mg/ml) admixed with CDDP (0.2 mg/ml) in NS was stable for only 24 h (Williams, unpublished data). On the other hand, CBP, like CDDP, might be expected to be influenced by an alkaline media. CBP (1 mg/ml) in 200 mM sodium bicarbonate or admixed with FU (10 mg/ml) in SW was unstable and decomposed within 12–24 h (Williams, unpublished data). Similarly, the dilution of a CBP (1 mg/ml) or CDDP (0.02 mg/ml) solution with MESNA (1 mg/ml) resulted in the rapid degradation of CBP and CDDP (Williams, unpublished data). The results of our studies indicate that CBP appears to exhibit instability and compatibility patterns similar to those of CDDP. Therefore, it is recommended that solutions of CBP not be stored in the presence of chloride ions, in alkaline media, or together with mesna-like (nucleophilic) substances and that their short-term storage in NS or chloride-containing solutions be limited to not more than 24 h. In light of the results obtained using CDDP and CBP, it is not unreasonable to suggest that other platinum complexes may pose similar compatibility problems.

Conclusion

Infusional chemotherapy has been increasingly used in clinical trials on the basis of the observations that most drugs have a relatively short half-life following bolus exposure and that increasing the available drug concentration over time may maximize the antitumor effect. As a practical matter, the application of infusional chemotherapy, especially in an ambulatory setting, absolutely requires that the individual agents remain stable in solution at room temperature (or at body temperature for implanted pump systems) and that the drugs be compatible.

The capacity to mix agents in a single solution facilitates the infusion of combinations of chemotherapeutics. Technologic advances are on the horizon that will provide a capability for the administration of multiple drugs through a single access site to allow the use of a single delivery source, thus obviating the need for admixtures of drugs. In the interim, admixtures represent the optimal method for the delivery of multi-agent chemotherapy in a setting in which continuous infusions can be carried out for 24 h or more. The data reviewed in this report summarize the extent of our knowledge of selected admixtures.

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