STABLE PHARMACEUTICAL SOLUTIONS OF VINCA ALKALOIDS

The vinca alkaloids are, in general, dimeric indole-dihydroindole compounds. Two of the alkaloids obtained from the leaves of the plant Vinca rosea, vincristine (VCR) and vinblastine (VLB), are marketed for the treatment of leukemias and related neoplasms in humans. A third compound, vindesine (VDS), an amide derivative of vinblastine, is marketed for the treatment of neoplastic diseases in humans in several European countries and is on clinical trial in the United States. These three drugs are described in United States Patents Nos. 3,205,220 (vincristine), 3,097,137 (vinblastine), and 4,203,898 (vindesine). The drugs are administered intravenously to patients suffering from susceptible neoplasms. The usual pharmaceutical formulation employed has been a lyophilized vial of a sulfate salt which is reconstituted prior to use. The sulfate salts are prepared by adding the theoretical amount of sulfuric acid to a solution of the alkaloidal free base. In the case of vindesine, however, the sulfate made by the ordinary procedure is not stable and a special sulfate salt disclosed in U.S. Patent 4,259,242 is employed in the lyophilized pharmaceutical formulation.

Researchers and medical personnel long have thought having ready-to-use solutions of vincristine sulfate or other vinca alkaloids would be desirable.

(10)

First, improper reconstitution of a lyophilized product sometimes results in the formation of air-borne droplets which may be a hazard to the hospital personnel who are making up the solution for an i.v. injection. Vincristine is an extremely potent oncolytic drug and avoiding contact with this drug so far as possible is desirable. Furthermore, avoiding all contact with any cytostatic drug and especially vincristine is desirable. In addition, a potential problem always exists during the reconstitution of a lyophilized formulation because an inappropriate quantity of diluent may be used or an incorrect amount of drug may be used because of a different vial size. The margin between toxic effects and therapeutic dose is very small with the vinca alkaloids. Errors in concentration for i.v. injection resulting in accidental overdosages with vincristine have been recorded in the literature. See, for example, the Journal of Pediatrics, 89, 671 (1976), Cancer Chemotherapy Reports, 55, 525 (1972), and Journal of Pediatrics, 90, 1042 (1977).

Another disadvantage of lyophilized vincristine sulfate arises from the mode of calculating dose levels for each individual. Vincristine sulfate is supplied in whole milligram amounts (e.g., 1 mg. and 5 mg. vials). Because a dose is usually calculated as 2 mg. per square meter of body surface for children and 1.4 mg. per square meter body surface for adults, the doses actually given are usually in decimal milligram amounts, and therefore only part of a vial's contents

(11)

may be used. In addition, it should be reiterated that there is a narrow margin between the toxic dose and the effective dose of vincristine. Thus, because the dosage usually is calculated for treating humans, there will ordinarily be some excess of reconstituted vincristine left over after a given treatment. This problem is not particularly serious in a large cancer clinic where there is a daily use of vincristine and that which is left from one patient may be applied to the next. However, the recommended life for reconstituted vincristine is 14 days at refrigerated temperature. Thus, in many instances, discarding excess reconstituted lyophilized vincristine which has outlived its 14 day dating period may be necessary. Vincristine is an extremely expensive drug and any amount of it which must be discarded will increase the overall cost of maintaining a cancer clinic.

Upon standing, the physical changes noticed for reconstituted lyophilized vincristine (reconstituted with 0.9% aqueous sodium chloride containing benzyl alcohol as a preservative) are a general haziness of solution followed by the appearance of a precipitate.

Another problem associated with reconstituted vincristine formulations is the need to incorporate a preservative in order to prevent the growth of microorganisms. In general, vincristine solutions cannot be heat sterilized but can be sterilized by filtration. However, even if the latter process is used, a pre-

(12)

servative must be present in the diluent used to reconstitute the lyophilized material or in an opened previously sterilized liquid vial because of the possibility of contamination from the air. Otherwise, the excess material would have to be discarded immediately and could not be kept even for the recommended maximum 14-day period.

Reconstituted solutions of vinblastine sulfate and vindesine sulfate possess similar problems and concerns although because both compounds contain an N-methyl group instead of the more labile N-formyl functionality found in vincristine, the stability problems are less severe as shown by the recommended reconstituted stability dating of thirty days.

In accordance with the present invention, a stable, ready-to-use solution of oncolytic vinca alkaloids for i.v. injection is provided. The use of these formulations minimizes the contact between hospital personnel and the drug and provides a single solution strength for all vial and syringe sizes employed thereby avoiding error in reconstitution.

In particular, in accordance with the invention, an aqueous pharmaceutical formulation which comprises a pharmaceutically-acceptable vinca dimer salt, a polyol, an acetate buffer, which maintains the pH of the solution between 3.0 and 5.0, and a preservative is useful as a stable oncolytic preparation.

This invention is particularly applicable to the preparation of stable, ready-to-use solutions of

(13)

vinca dimers, including vincristine sulfate, vinblastine sulfate and vindesine sulfate. The invention is useful also for the preparation of stable, ready-to-use solutions of certain vinca dimers which are presently on clinical trial or will shortly be on clinical trial as oncolytic agents. Among this second class of compounds are 4'-deoxy-1-formylleurosidine sulfate and leuroformine. This invention may also provide stable, ready-to-use solutions of other vinca dimers whose clinical use is not yet determined but which may be marketed as clinically useful oncolytic agents in the future.

The stabilized formulations of this invention are more applicable to, and useful with, N-formyl vinca dimers such as vincristine or 4'-deoxy-1-formylleurosidine because such compounds decompose by an additional mechanism, i.e., loss of the N-formyl group, not present with vinblastine or vindesine.

Pharmaceutically-acceptable salts other than the sulfate salt, such as the phosphate salt, may be used in the stable solutions of this invention although the sulfate salts are preferred. Pharmaceutically-acceptable salts are those salts useful in the chemotherapy of warm-blooded animals. The alkaloids usually are present in the formulation at a concentration of about 0.01 to 2.0 mg./ml., preferably at a concentration of 0.1 to 1.0 mg./ml.

The polyols useful in these stable, ready-to-use solutions of oncolytic vinca dimers are

(14)

generally those derived from sugars, such as mannitol and sorbitol, or are sugars themselves such as lactose and sucrose. Other useful polyols will be recognized by those skilled in the art. Lactose and especially mannitol are the preferred polyols used in this invention. The polyol usually is present in the formulation from about 10-100 mg./ml.

The acetate buffer system utilized in these stable solutions should maintain the pH in the range 3.0-5.0. The preferred pH ranges vary with the individual vinca alkaloid. In the case of vincristine sulfate, a pH range of 4.4-4.8 is preferred. For vinblastine sulfate, the preferred range is 3.8-4.2 and for vindesine sulfate, a pH range of 3.0-3.6 is preferred, especially the range 3.2-3.4. A buffer system with a molarity in the range of about 0.0005-0.02 M, preferably 0.002-0.01 M is used. The molar ratio of acetate to vinca dimer is preferably about 20 to 1 or less. In the case of vindesine sulfate, it will be recognized by those skilled in the art that, for pH's below 3.6, the "buffer" consists only of acetic acid and no acetate salt is employed. Although at pH 3.0 the acetic acid concentration approaches 0.06 M, at the preferred pH range of 3.2-3.4, the acetic acid concentration is about 0.02-0.01 M. The stabilizing effect of the acetate buffer may be due in part to preventing a pH change of the solution due to alkali leaching from the glass or stopper of the vial or from degradation due to the change of pH caused by

alkaloid decomposition.

In general, preservatives tested in solutions of vinca dimers have had a deleterious effect upon potency, clarity, and pharmaceutical elegance, but, of these, the parabens, methyl and propyl, seem to have little effect on these parameters and are therefore preferred. The parabens may be employed singly or in combination, usually in a total amount of 1-2 mg./ml. Other potential preservatives include benzyl alcohol, phenol, or m-cresol. The liquid formulations produced in this invention are sterilized by filtration.

In addition to the ingredients which are present in these sterile, stable solutions of the alkaloids, the chloride ion concentration should be minimized because chloride ion has a deleterious effect on the various oncolytic vinca dimers.

To further illustrate the invention, the following non-limiting Examples are provided.

Example 1

A stable, ready-to-use solution of vincristine sulfate is prepared as follows: a 1 mg. vial contains vincristine sulfate, 1 mg.; methyl paraben, 1.3 mg.; propyl paraben, 0.2 mg.; mannitol, 100 mg.; acetic acid, 0.0255 ml. of a 0.2 M solution; sodium acetate, 0.0245 ml. of a 0.2 M solution; water q.s. to 1 ml. Vials containing 2 mg. or 5 mg. of drug are prepared in similar fashion with proportionately larger amounts of materials. The solution thus prepared is

(16)

sterile filtered and introduced into compatible glass vials in the proper volume. The vials may be purged with an inert gas, such as nitrogen, before the vials are sealed with a compatible stopper.

Alternatively, hypodermic syringes of predetermined volume may be filled with the sterile filtered solution to provide a ready-to-use solution which is also ready to inject. Use of the pre-filled syringe further reduces the chance of exposure to patients or hospital or pharmacy personnel by eliminating the need to transfer a vial's contents to an empty syringe. Ideally, the syringe should be graduated and disposable.

Example 2

An example of a stable, ready-to-use solution of vinblastine sulfate contains the following ingredients: a 10 mg. vial contains vinblastine sulfate, 10 mg.; methyl paraben, 13 mg.; propyl paraben, 2 mg.; mannitol, 1000 mg.; acetic acid, 0.41 ml. of a 0.2 M solution; sodium acetate, 0.09 ml. of a 0.2 M solution; water, q.s. to 10 ml. The vials are processed in the same way as described above in Example 1. Hypodermic syringes as previously described may be filled with vinblastine solution.

Example 3

An example of a stable ready-to-use solution of vindesine sulfate contains the follcwing: for a 5 mg. vial or syringe, vindesine sulfate, 5 mg.; methyl

paraben, 6.5 mg.; propyl paraben, 1 mg.; mannitol, 500 mg.; acetic acid, 0.25 ml. of a 0.2 M solution; water, q.s. to 5 ml. The solution may be used to fill vials or syringes as described previously.

Example 4

Ready-to-use formulations of this type must be stable for periods allowing for distribution to the pharmacy and a reasonable shelf life. Vincristine sulfate formulations prepared according to this invention have remained physically and chemically acceptable for pharmaceutical use for periods up to one year at 5°C.

The formulations of this invention were evaluated for their stability by using analytical high pressure liquid chromatography and thin layer chromatography to determine vincristine content and quality. For example, three lots of formulated vincristine sulfate maintained 94-99% of their initial concentration after storage at 5°C. for about nine months. These three lots had the following composition: Vincristine sulfate, 1 mg./ml. of solution; methyl paraben, 1.3 mg./ml. of solution; propyl paraben, 0.2 mg./ml. of solution; mannitol, 100 mg./ml. of solution; acetic acid, 0.0255 ml. of a 0.2 M solution per ml. of solution; sodium acetate, 0.0245 ml. of a 0.2 M solution per ml. of solution; water, to volume. The solutions were sterile filtered and placed in amber type 1 acid treated vials which were then capped with

Teflon®-faced gray-butyl stoppers or Stelmi 632 stoppers. (Teflon® is the registered trademark of E.I. duPont de Nemours & Co., Inc. for polytetrafluoroethylene resins and products.) The final pH of the solution was approximately 4.6.

(19) * C L M S *

CLAIMS

1. An aqueous pharmaceutical formulation which comprises a pharmaceutically-acceptable vinca dimer salt, a polyol, an acetate buffer to maintain the pH of the solution between 3.0 and 5.0, and a preservative.

2. A formulation according to claim 1 in which the vinca dimer is vincristine, vinblastine, vindesine, 4'-deoxy-1-formylleurosidine or leuroformine.

3. An aqueous pharmaceutical formulation as claimed in claim 1 which comprises a pharmaceutically-acceptable vinca dimer salt, a polyol, an acetate buffer to maintain the pH of the solution between 3.5 and 5.0, and a preservative.

4. A pharmaceutical formulation as claimed in claim 1 or claim 3 in which the vinca dimer salt is a salt of vincristine.

5. A pharmaceutical formulation as claimed in claim 4 in which the polyol is a sugar or is derived from a sugar.

6. A formulation according to any one of claims 1 to 5 in which the preservative is methyl paraben and/or propyl paraben.

7. A formulation according to any one of claims 1 to 6 in which the concentration of the acetate buffer is 0.0005-0.02 M.

8. A formulation according to any one of claims 1 to 7 in which the polyol is mannitol or lactose.

9. A formulation according to any one of claims 1 to 8 containing per ml. of final solution about 1 mg. of vincristine sulfate, 10-100 mg. of mannitol or lactose, 1-2 mg. of a preservative

selected from methyl paraben and propyl paraben, singly or in combination, and water q.s. to 1 ml., with a pH of said solution between about 4.4 and 4.8 maintained by a 0.002-0.01 M acetate buffer.

10. A formulation according to claim 9 which contains, per ml. of final solution, about 1 mg. of vincristine sulfate, 100 mg. of mannitol, 1.3 mg. of methyl paraben, and 0.2 mg. of propyl paraben.

11. A formulation according to any one of claims 1, 2, 3 or 6 to 8 containing per ml. of final solution about 1 mg. of vinblastine sulfate, 10-100 mg. of mannitol or lactose, 1- 2 mg. of a preservative selected from methyl paraben and propyl paraben, singly or in combination, and water q.s. to 1 ml., with the pH of said solution being between about 3.8 and 4.2 maintained by a 0.01-0.002 M acetate buffer.

12. A formulation according to claim 11 which contains, per ml. of final solution, about 1 mg. of vinblastine sulfate, 100 mg. of mannitol, 1.3 mg. of methyl paraben, and 0.2 mg. of propyl paraben.

13. A formulation according to any one of claims 1, 2 or 6 to 8 containing per ml. of final solution about 1 mg. of vindesine sulfate, 10-100 mg. of mannitol or lactose, 1-2 mg. of a preservative selected from methyl paraben and propyl paraben, singly or in combination, and water q.s. to 1 ml. with pH of said solution between about 3.0 and 3.6.

14. A formulation according to claim 13 which contains, per ml. of final solution, about 1 mg. of vindesine sulfate, 100 mg. of mannitol, 1.3 mg. of methyl paraben, and 0.2 mg. of propyl paraben, with a pH of said solution between about 3.2 and 3.4.

15. A formulation for vinca dimers as claimed in claim 1 substantially as hereinbefore described with reference to any one of the Examples.