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X-RAY DETECTION OF CANCER WITH WATER-SOLUBLE SALTS OF IRON AND BISMUTH

Laurence G. Bodkin, New York, N.Y.
(558 E. 23rd St., Brooklyn, N.Y. 11210)

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5 Claims

ABSTRACT OF THE DISCLOSURE

Pharmaceutically acceptable solutions of iron and bismuth, desirably containing polyvinylpyrrolidone, are administered intravenously to form an X-ray contrast medium in cancerous tissue. The use of such solutions is of especial importance in the detection of cancers of the lower pelvic region.

This invention relates to processes for cancer detection and more particularly to processes utilizing X-ray photography in which the patient is first given a plurality of substances which interact in the body to give an X-ray contrast medium delineating cancerous tissue in the lower pelvic region.

Cancers of the lower pelvic region such as those of the rectum, sigmoid, and perineum, are frequently difficult to detect by present-day diagnostic techniques and particularly by diagnostic techniques employing X-ray photography. It is common practice in the diagnosis of cancer in the lower pelvic region to administer a barium enema and expose the region to an ordinary X-ray film. However, a barium enema frequently fails to show cancerous tissue in portions of the pelvic region other than the descending colon. Other diagnostic techniques also frequently fail to show cancers in the lower pelvic region. As a result, cancers of this region frequently go undetected until they are inoperable. A need exists for a new diagnostic technique which will permit the detection of cancers of the lower pelvic region at any early stage which will enhance the likelihood of successful treatment and arrest of cancerous growth.

It is an object of this invention to provide a new diagnostic technique which permits the discovery of cancers in the lower pelvic region at an early stage, increasing the likelihood of successful treatment. More specifically, it is an object of this invention to provide a process in which the patient is given a plurality of substances which interact in the body to form an X-ray contrast medium permitting detection of cancerous tissue in the lower pelvic region by ordinary X-ray photographic techniques.

According to this invention an iron compound and a bismuth compound, both in pharmaceutically acceptable solutions, are administered parenterally to the patient. Neither the iron compound nor the bismuth compound are X-ray contrast media in themselves, but these two compounds interact with the formation of an X-ray contrast medium which localizes itself in cancerous tissue in the body. The regions of the body undergoing diagnosis, and more especially the lower pelvic region, are then X-rayed by standard X-ray photographic techniques. It is nearly always desirable to admix a pharmaceutically acceptable solution of polyvinylpyrrolidone with the iron and bismuth solutions prior to administration in order to localize and prolong the action of the iron and bismuth compounds and to prevent their excretion.

The iron salts which are suitable for administration according to this invention include any of the iron salts which are known to be pharmaceutically acceptable for either oral or parenteral administration in the treatment of other ailments such as iron deficiency anemia. Water-

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soluble salts are preferred since water is the most convenient solvent for preparing injectable solutions. Examples of suitable iron salts are iron (ferric) cacodylate, ferric citrate, and ferrous gluconate. While ferrous sulfate may also be used, it is less desirable because of its astringent qualities. In general, the highly acidic and astringent iron salts should be avoided.

The bismuth salt may be any pharmaceutically acceptable bismuth salt, especially those salts which are presently known for the treatment of other ailments. Water-soluble bismuth salts are preferred since water is generally the preferred solvent for preparing injectable solutions. Bismuth sodium tartrate and bismuth sodium thioglycolate are examples of such water-soluble bismuth salts.

Although water is the preferred solvent for preparing the bismuth and iron salt solutions, other non-toxic solvents may be used if desired.

Both the iron and the bismuth salts are administered in dilute aqueous solutions, generally in concentrations of less than 5% by weight and most frequently in concentrations of about 1% to about 3% by weight. For example, a 1.3% aqueous solution of iron cacodylate and a 3% aqueous solution of bismuth sodium tartrate have been found eminently suitable for the purposes of this invention. The pH of the salt solution is preferably neutral or slightly acidic or basic, e.g., about 5 to 9. The solutions may be buffered to attain the desired pH.

Since both the iron and the bismuth salt solutions are prone to rapid excretion from the body, it is highly desirable and in fact virtually necessary to administer a substance which will cause retention of the bismuth and iron salts in the body and thus permit their accumulation and interaction to form an X-ray contrast medium which affords greater opacity to cancerous tissue than to normal tissue. Polyvinylpyrrolidone is the preferred material for this purpose. The average molecular weight of the polyvinylpyrrolidone may be anywhere in the range of about 20,000 to about 50,000. Excellent results are obtained with polyvinylpyrrolidone having an average molecular weight of about 40,000. On the other hand, it has been found that polyvinylpyrrolidone having an average molecular weight of only about 15,000 is ineffective to prevent excretion of the bismuth and iron salts. The polyvinylpyrrolidone is administered in aqueous solution. Solutions having a concentration of about 10% have been found to be well suited to the purposes of this invention. However, the concentration of the polyvinylpyrrolidone solution is not critical. It is well known that polyvinylpyrrolidone retards the release of medicaments, and that the extent of retardation is influenced by the molecular weight and the concentration of the polyvinylpyrrolidone.

For convenience in administration, the iron salt solution and the bismuth salt solution may be combined separately with solutions of polyvinylpyrrolidone. The iron salt and bismuth salt solutions should not be combined with each other, for a precipitate may be formed. Generally a far greater quantity of polyvinylpyrrolidone is mixed with the bismuth salt solution than with the iron salt solution. Thus, a typical unit dosage of iron may be formed by combining 5 cc. of 1.3% aqueous iron cacodylate with 15 cc. of 10% aqueous polyvinylpyrrolidone. A typical unit dosage of bismuth, on the other hand, may be formed by adding 5 cc. of 3% aqueous bismuth sodium tartrate to 500 cc. of 10% aqueous polyvinylpyrrolidone. Both the quantity of bismuth or iron salt and the ratio of bismuth or iron salt to polyvinylpyrrolidone in a unit dosage can be varied considerably. For instance, a unit dosage of iron may consist of 10 cc. or even 15 cc. of 1.3% iron cacodylate and 15 cc. of 10% polyvinylpyrrolidone. A unit dosage of bismuth may contain 2 cc. or 3 cc. of 3%

bismuth sodium tartrate and 15 cc. of 10% polyvinylpyrrolidone.

The amounts of both iron and bismuth salts may be varied widely and still give effective results. It has been found that as little as 5 cc. of 3% bismuth sodium tartrate, equivalent to about .10 to .11 gram of Bi, during the course of administration will be effective. More pronounced X-ray shadows are obtained with larger amounts, however. Much larger amounts of bismuth, up to about 42 cc. of 3% bismuth sodium tartrate during the course of administration, have been administered without ill effect. The amount of iron may also vary over wide limits. Effective results have been obtained with as little as 20 cc. of 1.3% iron cacodylate, equivalent to about 0.6 gram of Fe during the course of administration. More effective results are obtained with larger amounts of iron. Much larger amounts of iron, up to 140 cc. of 1.3% iron cacodylate during the course of administration, have been given without ill effect. The amount of iron and bismuth salts required for effective X-ray contrasts is dependent in large measure on the amount and the molecular weight of polyvinylpyrrolidone, as already indicated. The maximum amounts of iron and bismuth compounds are limited by the acute toxicities of these materials. The acute toxicities are known, since both the iron and bismuth salts are presently used as therapeutic agents for other purposes.

The iron and bismuth salt solutions are administered intravenously, preferably into a vein in the arm or leg.

The order of administration of the iron and bismuth salts is not critical. The bismuth salt is more frequently administered first, although the iron salt may be given first with good results. The entire amount of bismuth given during the course of administration may be administered in one day as a single unit dosage of 5 cc. of bismuth salt in 500 cc. of polyvinylpyrrolidone. This solution is preferably administered over a long period of time, e.g., 6 to 24 hours. Where more than 5 cc. of bismuth compound is to be given, the compound is best administered in a plurality of unit dosages on different days. The iron salt is generally given in a plurality of unit dosages, with only one unit dosage on any given day. Thus a patient receiving 20 cc. of iron salt will generally receive this salt in 4 unit dosages on 4 different days. Unit dosages of iron may contain as much as 15 cc. of 1.3% iron cacodylate or the equivalent amount of iron in other salts or other concentrations; seldom will a daily dosage exceed this amount. The iron salt may be administered more rapidly than the bismuth salt. The iron and bismuth compounds can be administered alternately if desired.

It generally requires about 2 to 6 weeks after an iron salt and a bismuth salt is first administered until the X-ray contrast medium is sufficiently formed in the body to afford effective contrast. After this period has elapsed, the patient may be subjected to ordinary flat plate X-ray photography of the region of the body where cancer is suspected. As previously indicated, this invention is particularly valuable in the diagnosis of cancer in the organs of the lower pelvic region, such as the rectosigmoid, sigmoid, and perineum, where previously known X-ray photographic techniques generally fail to show the presence of cancerous tissue. The exact mechanism by which the X-ray contrast medium is formed is unknown, but apparently an interaction occurs between the bismuth compound and the iron compound in the human body to form an X-ray contrast medium. This X-ray contrast medium appears to localize itself in cancerous tissue. Whether the X-ray contrast medium is formed in the cancerous tissue or is formed in other regions of the body and then transported to the cancerous tissue has not been determined.

The administration of iron and bismuth salts according to this invention is contraindicated in patients having elevated urea nitrogen or creatinine levels. Other contraindications for the bismuth and iron salts which are known in the art also apply in the case of the present invention.

The process of this invention provides a diagnostic technique which permits the detection of cancers of the lower pelvic region by conventional flat plate X-ray photography. This process permits early detection of cancer, greatly enhancing the likelihood of successful treatment and recovery of the patients.

This invention will now be described further with reference to the following specific examples.

In all of these examples, the bismuth solution was a 3% aqueous solution of bismuth sodium tartrate, buffered with sodium citrate and sucrose. The iron solution was a 1.3% aqueous solution of iron (ferric) cacodylate. The polyvinylpyrrolidone solution was a 10% aqueous solution of polyvinylpyrrolidone having an average molecular weight of 40,000.

In all of the following examples, the patient received two solutions. One was a bismuth-PVP solution, made by combining a 3% aqueous solution of bismuth sodium tartrate with 10% aqueous polyvinylpyrrolidone in the amounts indicated in each example. The second was an iron-PVP solution, made by combining a 1.3% aqueous solution of iron (ferric) cacodylate with 10% aqueous polyvinylpyrrolidone in the amounts indicated. All solutions were administered intravenously in either the arm or the leg.

EXAMPLE 1

Patient A, a male, 59 years old, with history of loose bowel movements for 12 months, underwent resection of the descending colon for obstructing carcinoma with extensive metastasis of the peritoneum, liver, and mesenteric nodes. Three months later he was again admitted to the hospital, in late stages, for palliative treatment. On the first 3 days a solution of 15 cc. of PVP and 5 cc. of iron cacodylate was administered intravenously. No solution was given on the 4th day, and on the 5th day the patient was given a solution of 500 cc. of PVP and 5 cc. of bismuth sodium tartrate, administered over a period of 24 hours. No solution was given on the 6th through 8th days. On the 9th day the patient again received 15 cc. of PVP and 5 cc. of iron cacodylate. A barium enema study 5 days later showed a deformity only in the region of the previous resection of the descending colon. However, a flat plate study done about 2 months later (11 weeks after the first administration of PVP and iron cacodylate) showed a large clearly defined opaque shadow in the lower abdomen, representing a metastatic carcinomatous mass. The patient died a few days later. An autopsy confirmed the fact that the mass seen in the X-ray flat plate study was carcinomatous.

EXAMPLE 2

Patient B, a male, 61 years of age, was admitted to the hospital with a diagnosis of carcinoma of the rectum and possible carcinoma of the sigmoid. This patient had a history of irregular bowel movements and occasional rectal bleeding for one year and a history of removal of malignant polyps of the rectum 7 or 8 years earlier. The patient received 500 cc. of PVP and 5 cc. of bismuth sodium tartrate through intravenous tubes for a period of 10 hours. On the 4th through 7th days, the patient received 15 cc. of PVP and 10 cc. of iron cacodylate each day. Administration of PVP and iron cacodylate was omitted on the next day, and on the following day the patient received 500 cc. of PVP and 30 cc. of iron cacodylate continuously through intravenous tubes over a period of 24 hours. X-rays showed no shadow at this time. Five weeks later, another X-ray showed a clearly defined mass in the rectosigmoid as well as a shadow in the rectum. An abdominal plate was not taken. Surgery was done in stages because of obstructions and the patient's poor condition. The carcinoma of the sigmoid was removed. Later an abdominoperineal resection was done. The excised specimen showed separate lesions in the rectum and rectosigmoid as seen in the second X-ray studies. The patient made an uneventful recovery.

5 EXAMPLE 3

Patient C, a female, 52 years old, was admitted to the hospital. This patient had previously undergone resection of the rectosigmoid and an abdominoperineal resection for carcinoma. A recurrence in the perineum had been treated by chemotherapy for over a year. Flat plate X-ray films made 2 months after the start of chemotherapy showed nothing. Upon admission to the hospital the patient received 500 cc. of PVP and 5 cc. of bismuth sodium tartrate, administered intravenously over 24 hours, on the 1st day. Two days later the patient received 500 cc. of PVP and 20 cc. of iron cacodylate. On the following day, 500 cc. of PVP and 5 cc. of bismuth sodium tartrate were administered over 24 hours. Flat plate X-rays were negative. Twenty-nine days after the initial administration of PVP and bismuth solution, the patient received 500 cc. of PVP and 20 cc. of iron cacodylate, followed by 500 cc. of PVP and 5 cc. of bismuth on the next day and by 500 cc. of PVP and 20 cc. of iron cacodylate 4 days after the initial administration of PVP and iron. Flat plate X-rays taken 2 days later showed an opaque, well circumscribed shadow in the lower pelvis. Chemotherapy followed by deep X-ray therapy were administered. The patient is still living.

EXAMPLE 4

Patient D, a female, 72 years old, was admitted to the hospital with a large inoperable carcinoma of the rectum with metastasis to the liver. Chest X-ray showed pulmonary metastases. The patient received intravenously alternate injections of PVP (15 cc.) and 5 cc. of iron cacodylate followed by 15 cc. of PVP and 2 cc. of bismuth sodium tartrate daily, for 9 consecutive days. About 1 month later the patient again received alternate injections of PVP and iron and PVP and bismuth, in the same amounts, on 9 successive days. Flat plate X-ray studies made 3 days after the end of the first series of 9 injections were negative. Faint shadows were observed in flat plate X-ray studies made 1 month after the second series of injections. A third set of flat plate studies, made 3 months after the second series of injections showed definite opacities outlining the rectal carcinoma. The patient died 9 months later.

EXAMPLE 5

Patient E, a female, 67 years old, was admitted to the hospital when a small recurrence of a previously cauterized small localized carcinoma of the posterior rectal wall was found. On the 1st day the patient received 15 cc. of PVP and 10 cc. of iron cacodylate. The next day the patient received 500 cc. of PVP and 5 cc. of bismuth sodium tartrate over a period of 24 hours. Administration was omitted on the 3rd day and on the 4th and 5th days the patient received 15 cc. of PVP and 10 cc. of iron cacodylate each day. One month later, small but definite shadow was seen in the region of the lesions in a flat plate X-ray film. A resection was done later.

EXAMPLE 6

Patient F, a female, 66 years old, had a large recurrent mass in a perineal wound following an abdominoperineal resection for carcinoma of the rectum 4 months previously. On the 1st day, the patient received a dose of 15 cc. of PVP plus 3 cc. of bismuth sodium tartrate followed the next day by 15 cc. of PVP and 10 cc. of iron cacodylate. This alternate dosage was continued for 14 days. At

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the end of this time, X-ray film showed a faint soft tissue shadow. The patient died approximately 1 month later.

EXAMPLE 7

Patient G, a female, 41 years of age, was given 15 cc. of PVP and 15 cc. of iron cacodylate on 3 successive days following admission to the hospital. This was followed by 500 cc. of PVP and 5 cc. of bismuth sodium tartrate, administered over a period of 6 hours, 2 days later. Administration was omitted the next day, and on the following day the patient received 15 cc. of PVP and 3 cc. of bismuth sodium tartrate. A flat plate X-ray study 3 days later was negative. Two days after the X-ray study, a sigmoid colostomy was done, since a large fixed rectal mass was found under the pelvic peritoneum with metastasis to both lobes of the liver. An X-ray film taken 2 weeks after the sigmoid colostomy showed a large oval sharply delineated density in the lower pelvis. The patient was free of symptoms 6 months later.

What is claimed is:

1. A process for detecting cancerous tissue in a patient, said cancerous tissues being selected from the group consisting of cancers of the perineum, rectum, rectosigmoid and sigmoid, which process comprises administering intravenously to said patient an effective amount of an aqueous solution of a bismuth salt selected from the group consisting of bismuth sodium tartrate and bismuth sodium thioglycollate and polyvinylpyrrolidone of an average molecular weight of about 20,000 to about 50,000, and an effective amount of an aqueous solution of an iron salt selected from the group consisting of iron cacodylate, ferric citrate, ferrous gluconate and ferrous sulfate and polyvinylpyrrolidone of an average molecular weight of about 20,000 to about 50,000, said bismuth and iron salts being administered separately, and about 2 to 6 weeks after the first administration taking an X-ray photograph of the area of said patient undergoing diagnosis.

2. A process according to claim 1 wherein the minimum amount of said bismuth salt is about 0.10 gram calculated as Bi and the minimum amount of said iron salt is about 0.06 gram calculated as Fe.

3. A process according to claim 2 wherein said iron salt is iron cacodylate and said bismuth salt is bismuth sodium tartrate.

4. A process according to claim 1 wherein said iron salt is the first administered.

5. A process according to claim 1 wherein said bismuth salt is the first administered.

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ALBERT T. MEYERS, Primary Examiner

V. C. CLARKE, Assistant Examiner

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