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Peptic Ulcer Disease and Other Complications in Patients Receiving Dexamethasone Palliation for Brain Metastasis

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A retrospective analysis was done of 106 patients who received radiation therapy for brain metastasis. Dexamethasone therapy was instituted in 97 patients. Peptic ulcer disease developed in 5 of 89 patients (5.6 percent) who received a dosage of at least 12 mg a day, but did not occur in patients who received a lower dose or in those who did not receive steroids. The interval between institution of dexamethasone therapy and the development of peptic ulcer disease ranged from three to nine weeks. Two patients had perforated ulcers, one of whom required surgical resection. Peptic ulcer disease contributed to the general deterioration and death of three of the five patients. Overall, in 14 of the 89 patients (15.7 percent) a complication of steroid therapy developed in the form of peptic ulcer disease, steroid myopathy or diabetes mellitus (or a combination of these).

CORTICOSTEROIDS HAVE BEEN SHOWN to be extremely effective in relieving the symptoms of cerebral edema due to primary or metastatic tumors in the brain.[1-3] Dexamethasone is one of the most commonly used agents. Side effects and complications of steroid therapy are recognized and one of the major potential complications associated with corticosteroid therapy is the development of peptic ulcer disease.[4,5] We review the use of dexamethasone in patients receiving radiation therapy for brain metastasis and the subsequent appearance of peptic ulcer disease and other complications.

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Patients and Methods

A retrospective analysis was done of patients at the City of Hope National Medical Center who received radiation therapy for brain metastasis between June 1977 and June 1981. Excluded from analysis were patients who received radiation therapy to the brain for hematologic malignancies, meningeal carcinomatosis, skull metastasis without intracranial disease or small cell undifferentiated bronchogenic carcinoma without intracranial disease.

There were 106 patients available for review,

TABLE 1.—*Patients With Brain Metastasis Distributed According to Primary Site*

Primary Tumor Site	Number of Patients
Lung	38
Breast	24
Skin (melanoma)	11
Gastrointestinal tract	10
Genitourinary tract	10
Head and neck	4
Other (thymus, cervix, pleura, bone)	4
Unknown primary	5
TOTAL	106

50 of whom were male and 56 female. The age of the patients ranged from 11 to 81 years with an average age of 54 years. Table 1 shows the distribution of patients by the primary site of the cancer.

Brain metastasis was diagnosed in all patients by radionuclide brain scan, computerized tomography or cerebral angiography (singly or in combination). Diagnosis of a malignant neoplasm was confirmed by pathology studies in all patients. Five patients underwent craniotomy as the initial treatment. All patients received radiation therapy to the entire brain, a broad range of dose schedules being used. Anticonvulsant medication was administered to 17 patients. Misonidazole (an experimental orally given drug related to the antiprotozoal agent metronidazole) which is currently being evaluated as a potential agent to increase the radiosensitivity of tumors was concurrently given to six patients who were receiving treatment according to protocols of the Radiation Therapy Oncology Group.

Dexamethasone therapy was instituted in 97 patients at the time of diagnosis of brain metastasis and was the only corticosteroid used. The standard dose was 4 mg given orally every six hours. The total dosage was at least 12 mg per day in 89 patients and 8 mg or less a day in eight patients. Nine patients with minimal or no neurologic symptoms did not receive steroid therapy. In only one patient was therapy started with a dosage of greater than 24 mg a day. The daily dosage was increased to greater than 24 mg in several patients whose neurologic symptoms worsened while they were receiving radiation therapy. Dexamethasone administration was continued during the course of radiation therapy until it was judged that a sufficient radiation dose had been delivered for tumor shrinkage to occur. This was a minimum of two weeks in most patients. The dexamethasone dosage was then gradually tapered during a period of one to three weeks until administration of the drug was discontinued. Many patients, however, required steroid therapy on a long-term basis to suppress persistent neurologic symptoms.

All patients were observed for a minimum of three months after the institution of dexamethasone therapy. Statistical significance was tested by the x^2 method.[6]

Results

In 5 of the 89 patients (5.6 percent) receiving at least 12 mg of dexamethasone a day peptic ulcer disease developed (Table 2). This complication did not occur in patients who received a lower dosage of dexamethasone or in those who received no steroid therapy. The five patients in whom peptic ulcer disease developed ranged in age from 42 to 60 years; three were men and two were women. Four of the five had known distant metastasis at sites other than the brain. All five had received systemic chemotherapy, three concurrently at the time of diagnosis of brain metastasis and two at some time in the past. Presenting neurologic symptoms in three patients were either mild or controllable by nonsteroid medication given orally. These included headaches, nausea, vomiting, seizures and transient visual auras. One patient had mild right hemiparesis and aphasia. Another patient had symptoms of vertigo, incoordination and confusion. None of the five patients were stuporous, somnolent or comatose. Four of the five had multiple metastatic lesions in the brain. None, however, had massive lesions producing either midline shift or obstructive hydrocephalus. Metastatic lesions were located solely in the cerebral hemispheres in four patients and in both the cerebrum and cerebellum in one. In one patient, the metastatic lesions were found to be due to direct invasion from skull lesions, whereas in the other four patients they were considered to be hematogenously transmitted. None of the five patients underwent craniotomy at any time during their clinical course.

The interval between the institution of dexamethasone therapy and the development of peptic ulcer ranged from three to nine weeks. In only one patient did an ulcer appear in less than six weeks. Two of the five patients were prophylactically placed on antacids while receiving steroids.

TABLE 2.—*Patients in Whom Peptic Ulcer Disease (PUD) Developed After Receiving Dexamethasone*

Case	Age/Sex	Primary Tumor: Site	Primary Tumor: Histologic Diagnosis	Interval From Primary to Brain Metastasis (mos)	Dexamethasone: Total Daily Dose (mg)	Dexamethasone: Duration to PUD (wks)	Symptoms of PUD	Peptic Ulcer: Site	Peptic Ulcer: Perforation	Survival Status After PUD Diagnosis
1	42/♀	Lung	Small cell	0	16	3	Pain × 8 days	Gastric	No	Died 8 mos
2	52/♂	Prostate	Adenocarcinoma	40	16	6	Sudden onset of pain	Duodenal	Yes	Died 2 mos*
3	56/♂	Lung	Adenocarcinoma	56	16	8	Sudden onset of pain	Gastric	Yes	Died 2 mos*
4	51/♂	Skin	Melanoma	80	24	7	Lower gastrointestinal tract bleeding	Duodenal	No	Died 2 wks*
5	60/♀	Breast	Adenocarcinoma	22	12	9	Pain × 7 days	Gastric	No	Died 8 mos

*Peptic ulcer disease contributed to general deterioration and demise of patient.

Tapering of dexamethasone dosage had been started in two patients before the peptic ulcer disease developed.

Possible associated factors were noted in four patients, including three who were using aspirin, aspirin-containing medication or indomethacin for pain relief, two patients who had thrombocytopenia, and one patient who had a history of prolonged ethanol abuse. One patient reported a history of peptic ulcer disease, though this could not be confirmed.

Symptoms were sudden onset of severe epigastric pain in two patients, epigastric pain of several days' duration in two patients and bleeding per rectum in one patient. Three patients had gastric ulcers and two had duodenal ulcers. The diagnosis was made by upper gastrointestinal x-ray series in four cases and by exploratory laparotomy in one. Both patients with abrupt onset of pain had perforated ulcers, one a gastric ulcer and the other a duodenal ulcer. Four were treated by nonsurgical means, including administration of antacids, cimetidine, blood transfusions or antibiotics (or a combination of these). The patient who had an exploratory laparotomy was found to have a perforated gastric ulcer and underwent a Bilroth-II procedure with resection of 70 percent of the stomach. Ulcers resolved in two patients, but contributed to the general deterioration and demise of the other three patients.

Further analysis of the 89 patients who received at least 12 mg of dexamethasone a day showed that neither misonidazole nor anticonvulsant medication produced a statistically significant difference in the frequency of peptic ulcer disease. This complication occurred in one of six patients (16.7 percent) who received misonidazole and in 4 of 83 patients (4.8 percent) who did not. It developed in 1 of 13 patients (7.7 percent) who received anticonvulsants and in 4 of 76 (5.3 percent) who did not.

Other complications of long-term steroid therapy were found. Steroid myopathy was diagnosed in four patients. The development or exacerbation of diabetes mellitus (that is, symptomatic hyperglycemia requiring medical treatment) occurred in six patients. Three of the six had a history of adult-onset diabetes mellitus. One patient suffered both myopathic and diabetic complications. All patients with these two complications had received at least 12 mg of dexamethasone a day. Overall, in 14 of the 89 patients (15.7 percent) taking at least 12 mg of dexamethasone a day, a complication of steroid therapy developed in the form of peptic ulcer disease, steroid myopathy or diabetes mellitus.

Discussion

Peptic ulcer disease and gastrointestinal bleeding are recognized complications of corticosteroid therapy.[2,4,5] Their development has been evaluated in detail in neurosurgical patients. Peptic ulcer disease may appear as stress ulcers following craniotomy in patients with intracranial disease.[7] It occurs more frequently, though, when neurosurgical patients are also receiving steroids. Gastrointestinal bleeding has been reported in 0.3 percent to 4.0 percent of patients not receiving steroids and in 1.5 percent to 16.5 percent of patients receiving steroids.[7-9] The duration of steroid administration in neurosurgical patients is usually seven to ten days. Gastrointestinal bleeding occurred mainly in comatose, respirator-dependent patients who required steroids for more than ten days.[7,9] Gastrointestinal bleeding may have been the result of the stress of the respirator,

but may also have been the result of a prolonged course of steroid therapy.

Peptic ulcer disease has also been reported in patients with neurologic diseases who did not undergo craniotomy. Ottonello and Primavera[10] showed in an autopsy study that in patients with acute cerebrovascular accident, there was a greater incidence of peptic ulcers in those who received steroids than in those who did not. Graham and Caird[11] noted that peptic ulcer disease developed in 1 of 20 patients who received steroids to palliate the symptoms of a brain tumor. Greenberg and co-workers[12] noted a 1.2 percent incidence of peptic ulcer disease in patients receiving steroids while undergoing radiation therapy for spinal cord compression due to epidural metastatic cancer. They used dexamethasone in a regimen that started with a dosage of 96 mg a day, which was then rapidly tapered and its use discontinued in two weeks.

The present study shows an incidence of peptic ulcer disease of 5.6 percent in patients receiving a dosage of dexamethasone of at least 12 mg a day. This complication appeared in patients who were ambulatory with only mild to moderate neurologic symptoms and who had not undergone craniotomy. It appeared only in patients who required that a dosage of at least 12 mg of dexamethasone a day be maintained for several weeks. This complication is serious because it may appear suddenly in the form of a perforated viscus and may lead to the deterioration and death of a patient.

The concurrent use of anticonvulsant medication or the radiosensitizer agent misonidazole did not appear to alter the incidence of peptic ulcer disease. Concurrent use of known ulcerogenic agents such as aspirin or indomethacin may increase the risk of a peptic ulcer developing.

In summary, dexamethasone and other corticosteroids are highly effective for rapidly palliating the symptoms of brain metastasis. Yet, because of the risk of the potentially serious complications of peptic ulcer disease, diabetes mellitus and steroid myopathy, corticosteroid dosage should be tapered and administration eventually discontinued as soon as radiation therapy has provided symptomatic relief. For patients with minimal or no neurologic symptoms, the use of steroids should be considered carefully in view of the risk of complications.

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