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Corticosteroids in terminal cancer—a prospective analysis of current practice

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Summary

Over half of a group of 373 inpatients with advanced malignant disease were treated with corticosteroids for a variety of reasons. They received either prednisolone or dexamethasone, or replacement therapy with cortisone acetate. Forty percent of those receiving corticosteroids benefited from them. A higher response rate was seen when corticosteroids were prescribed for nerve compression pain, for raised intracranial pressure, and when used in conjunction with chemotherapy. No significant difference in efficacy was noted between the 2 drugs. The results, however, suggest that with a larger sample, dexamethasone would have been shown to be significantly better than prednisolone in the management of nerve compression pain.

The incidence of side effects was broadly similar with dexamethasone and prednisolone. The most common side effect was oral candidosis and there was a highly significant relationship between the use of corticosteroids and the prescription of nystatin suspension. Dexamethasone was more likely than prednisolone to cause oro-pharyngeal candidosis. Dexamethasone was also associated with significantly more cases of psychological disturbance and hyperactivity. On the other hand, dexamethasone seems less likely to cause oedema, weight gain and dyspepsia. Corticosteroids were withdrawn because of side effects in only 11 patients (5%)—6 were receiving dexamethasone and 5 prednisolone. Dexamethasone has been adopted as the standard corticosteroid for terminal cancer patients at Sir Michael Sobell House.

KEY WORDS: terminal cancer, corticosteroids, symptom control.

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Introduction

Corticosteroids have a major role to play in the control of symptoms in patients with advanced malignant disease. They may be employed in a non-specific way to improve mood and appetite; or they may be indicated as specific adjunctive therapy in the relief of symptoms related to a large tumour mass or to nerve compression. The management of a number of other symptoms and syndromes may also be facilitated by treatment with corticosteroids (Table 1).

The use of corticosteroids in patients with advanced cancer is empirical, as it is in other non-endocrine indications. There is little published information on practical aspects of treatment with these drugs in such patients, and a notable lack of guidance in textbooks on therapeutics or chemotherapy.

There is only one published report of a controlled study of corticosteroids in patients with advanced cancer. Dexamethasone was shown to produce a significant improvement in appetite and strength, compared with placebo, in just over half of the patients who received it (Moertel *et al.*, 1974). A systematic evaluation of the risk-benefit ratio of corticosteroids in advanced cancer based on post-mortem findings revealed that the risks of major toxic events is small and is far outweighed by the benefits (Schell, 1966, 1972).

There are no published clinical data on the incidence of less serious side effects, or on dosage, relative efficacy and specific indications for the commonly used oral corticoids. To obtain such information, we have carried out a prospective review of our current practice with corticosteroids in patients who have advanced malignant disease.

Patients and methods

The survey involved patients admitted to Sir Michael Sobell House, a continuing care (hospice)

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TABLE 1. Indications for corticosteroids in patients with terminal cancer

Non-specific uses	As a co-analgesic	Specific uses
To improve appetite	Raised intracranial pressure	Hypercalcaemia
To enhance mood	Nerve compression	Carcinomatous neuropathy
To improve strength	Hepatomegaly	Spinal cord compression
To reduce fever	Head and neck tumour	Superior vena cava obstruction
	Intrapelvic tumour	Airways obstruction
	Abdominal tumour	Carcinomatous lymphangitis
	Retroperitoneal tumour	Haemoptysis
	Lymphoedema	Leuco-erythroblastic anaemia
	Metastatic arthralgia	Malignant effusion
		As adjunctive chemotherapy
		To minimize radiation-induced reactive oedema
		Discharge from rectal tumour (used locally)

unit at the Churchill Hospital, Oxford. Consecutive patients were included and all those who received treatment with corticosteroids during the course of their admission were carefully monitored. A specially designed record sheet was completed on admission and updated throughout the patient's stay in the ward. The patient's name and diagnosis were recorded together with details of corticosteroid therapy, the drug used, the dose and duration of use and the specific indication.

A check list of indications was provided on the sheet and is shown in Table 1 (derived from Twycross, 1981), together with a check list of possible adverse effects. The record forms were usually completed or updated during the course of the main weekly ward round or in the daily doctor-sister report session. Whenever there was doubt about the reason for prescription, this was clarified with the physician who had first prescribed the drug. In a few instances, an assumption about the precise indication had to be made on the basis of information in the patient's clinical notes.

Each time the record form was updated, the response of the patient to the corticosteroid was assessed and a note was made of any adverse effects. Judgement of response was based on the clinical impression of the physicians and of the nursing staff who were looking after the patient.

Results

The survey covered a period of 16 months, from September 1980 to December 1981. During that time, 373 patients were admitted (115 on more than one occasion); 218 (58%), of whom 124 were female, received corticosteroids. A wide range of primary sites were included and also 2 patients with non-malignant disease. The most common sites were breast (45 cases), bronchus (32), colon (21), prostate (13) and stomach (9). Also well represented were cancer of the kidney (7), cervix (7), ovary (6), brain (6), rectum (6), bladder (5) and pancreas (5).

The usual starting dose of prednisolone was 10–30 mg daily in divided doses ($n=121$) and of dexamethasone 4–16 mg a day ($n=68$; 27 patients started on 4 mg or less). The higher doses of dexamethasone were mainly used for raised intracranial pressure or spinal cord compression (4 mg tds or qds). This indicates that, in general, the dose of dexamethasone employed was considerably greater than an equivalent dose of prednisolone (4 mg dexamethasone being approximately equipotent with 30 mg prednisolone). The maintenance dose varied considerably between patients: from 5 mg to 20 mg prednisolone daily, or 0·5 mg dexamethasone on alternate days to 4 mg twice daily.

Table 2 shows the indications for the use of corticosteroids and an assessment of the patients' response. In a number of patients, more than one indication was applicable and an attempt was made to monitor progress for each individually. Chi-square analysis reveals no statistically significant differences between the response rates for the two drugs either overall, or when particular indications are examined separately.

There is one indication for which dexamethasone seemed to be more effective than prednisolone, though the figures do not achieve statistical significance. This was in the management of nerve compression pain. Since higher doses of dexamethasone were used (4 mg daily, $n=7$; 8 mg, $n=4$; 16 mg, $n=2$) compared with the doses of prednisolone (30 mg daily, $n=10$; 20 mg or less, $n=11$) this apparent superiority may be merely a manifestation of a dose response relationship and by itself is of questionable clinical significance. However, when viewed in the light of the incidence of side effects it assumes much greater importance.

There were no other indications where both drugs were used sufficiently frequently to make valid comparisons about efficacy.

TABLE 2. Indications for use and response

Indications	Prednisolone		Dexamethasone	
	n	Responders (%)	*n*	Responders (%)
Non-specific 'tonic'	58	22 (38%)	17	7 (41%)
Nerve compression	21	8 (38%)	13	8 (62%)
Chemotherapy	25	15 (60%)	2	1
Raised intracranial pressure	1	0	23	10 (43%)
Airways obstruction	15	5 (33%)	2	0
Metastatic arthralgia	6	3 (50%)	1	0
Paraparesis	0	0	6	0
Retroperitoneal tumour	6	0	0	0
Intrapelvic tumour	2	1	3	1
Hypercalcaemia	3	3	2	2
Lymphangitis	3	0	0	0
Head and neck tumour	2	1	1	0
Abdominal tumour	2	0	1	1
Hepatomegaly	0	0	3	2
Lymphoedema	1	0	1	1
Malignant effusion	2	0	0	0
Obstructive jaundice	2	0	0	0
Dysphagia	2	1	0	0
Proximal myopathy	1	1	0	0
Peripheral neuropathy	1	0	0	0
Others	6	3	2	1
Total	159	63 (40%)	77	34 (44%)

Side effects attributed to treatment with prednisolone or dexamethasone are shown in Table 3. The figures are similar in terms of the total number of side effects observed and Chi-square analysis again shows no significant difference between the two drugs overall. Nor is there any significant difference in the incidence of the most common adverse effects of oropharyngeal candidosis, oedema, facial mooning and dyspepsia (though there is a trend for more cases of candidosis to be associated with dexamethasone).

Oro-pharyngeal candidosis is endemic in hospices and is also a well recognized adverse effect of corticosteroids. Our usual first-line treatment is nystatin suspension and one way of looking at the problem of candidosis is to examine the prescriptions of nystatin. Of 373 patients admitted to the Unit during the course of the survey, 104 (28%) received nystatin at some stage. Of these, 81 patients (78%) were receiving steroids (40 dexamethasone, 38 prednisolone and 3 cortisone acetate). There is an highly significant relationship between the prescription of corticosteroids and the need for nystatin ($\chi^2 = 22{\cdot}44$, $P < 0{\cdot}001$).

The only statistically significant differences between the two drugs relate to two of the less common side effects. Dexamethasone caused significantly more psychological changes ($\chi^2 = 5{\cdot}60$ using Yates correction, $P < 0{\cdot}02$) and hyperactivity ($\chi^2 = 4{\cdot}65$ using Yates correction, $P < 0{\cdot}05$).

In 11 patients, treatment with corticosteroids had to be discontinued because of the severity of side effects. In the case of dexamethasone these were: hypomania (2), Cushingoid appearance (2), acneiform rash (1) and myoclonic jerks (1); and for prednisolone: Cushingoid appearance (1), dyspepsia (1), oedema (1), insomnia (1) and one patient with multiple side effects.

The duration of treatment with corticosteroids ranged from one day to almost 11 years: the median duration was between 4 and 8 weeks.

TABLE 3. Side effects

	Prednisolone ($n = 146$)	Dexamethasone ($n = 109$)
Candidosis	38 (26)*	40 (37)
Oedema	30 (21)	20 (18)
Moon face	22 (15)	23 (21)
Dyspepsia	11 (8)	7 (6)
Psychic changes	2 (1)	9 (8)
Weight gain	7 (5)	4 (4)
Eccymoses	4 (3)	5 (5)
Hyperactivity	0	5 (5)
Glycosuria/hyperglycaemia	0	4 (4)
Insomnia	3 (2)	3 (3)
Hyperphagia	1 (1)	3 (3)
Myopathy	2 (1)	2 (2)
Myoclonic jerks	0	2 (2)
Skin rash	0	2 (2)
Osteoporosis	1 (1)	0
Vomiting	1 (1)	0
Cataract	0	1 (1)

*Number in parentheses = %.

Discussion

The value of corticoids in patients with advanced or terminal malignant disease has become increasingly recognized in recent years (Baines, 1978). There is still, however, a widespread reluctance to use these drugs in the absence of obvious traditional indications. This is partly because of their well-known serious toxic effects and partly due to a lack of appreciation of their potential benefit in terminal cancer. It is also a reflection of the absence of detailed information on the incidence and severity of adverse effects.

Prednisone is a synthetic analogue of cortisone and is converted in the liver to prednisolone. There is no reason to use prednisone in preference to prednisolone and this latter drug has become the most widely used oral corticosteroid in non-endocrine indications. It has predominantly glucocorticoid effects and is 5 times more potent than cortisone in terms of anti-inflammatory activity, but causes less sodium retention.

Dexamethasone is also synthetic. It has approximately 7 times the anti-inflammatory activity of prednisolone but only slight mineralcorticoid activity (Haynes and Murad, 1980). In other respects, dexamethasone and prednisolone seem to be identical (Boland, 1958a; 1958b; Bunim *et al.*, 1958). In particular, the early studies showed a similar incidence of side effects with the two drugs.

Dexamethasone has become widely used for the treatment of raised intracranial pressure resulting from a variety of causes, and for spinal cord compression. The reason that dexamethasone is chosen in these situations seems to be simply that the first report of the use of corticosteroids in the treatment of cerebral oedema associated with brain tumours and brain surgery involved this drug (Galicich and French, 1961). The authors of the original report used dexamethasone because of its potent anti-inflammatory activity and relative lack of sodium and water retaining properties. Other reports have indicated that prednisolone is just as effective in this indication (King, Moon and Brown, 1965). There have been no comparative studies to show that in equivalent doses dexamethasone has a more specific effect than prednisolone in the treatment of cerebral oedema or indeed that any of the synthetic corticosteroids possess special properties which make them particularly appropriate for systemic therapy in specific indications.

At the time of the survey, the usual choice of corticosteroid in Sir Michael Sobell House was soluble prednisolone, except in certain circumstances when dexamethasone was used instead. These were: the management of patients with raised intracranial pressure, spinal cord compression, or uncomplicated nerve root compression, and the treatment of patients with compromised cardiac function or marked oedema from other causes. The choice of soluble prednisolone as our 'standard' drug was on the grounds of familiarity, patient acceptability and, we believed, cost. We have subsequently discovered that we had mistakenly equated the cost of the *soluble* tablet with that of the standard non-soluble preparation. The soluble form is, in fact, *36 times* more expensive (in the Oxford hospitals) and is 5 times more expensive than dexamethasone in equivalent doses.

Prednisolone and dexamethasone are not suitable by themselves as replacement therapy in patients who have had an adrenalectomy or hypophysectomy as they have relatively little mineralcorticoid activity. For this reason cortisone acetate is still commonly used when replacement therapy is indicated.

The drugs were initially prescribed in an high enough dose to be sure that any treatment effect would not be missed. In the absence of any response, the dose was reduced and the drug then discontinued. In those patients who did show a response, the dose was reduced to a maintenance level which was arrived at empirically by balancing continuing benefits against an acceptable level of side effects for individual patients.

The response rates for the most common indication, the non-specific 'tonic' effect, are very similar and are of considerable clinical significance. They represent a major benefit in terms of symptomatic improvement in a group of patients often intractable to other measures.

The 100% response rate in the treatment of hypercalcaemia is misleading. Patients with hypercalcaemia admitted to Sobell House virtually never respond to a single measure, and are invariably managed with a combination of some or all of rehydration, corticosteroids, oral phosphate, and intravenous mithramycin. All of the patients in this survey received one or more of these other specific measures for their hypercalcaemia in addition to treatment with corticosteroids.

It is notable that none of the 6 patients with spinal cord compression treated with dexamethasone showed an improvement. However, we have recently used dexamethasone in high dosage (6 mg every 4 hr) in the treatment of a patient with early spinal cord compression. She showed a definite response in terms of relief of pain but no improvement in function. Others have advocated the use of much higher doses of dexamethasone, with an initial bolus of 100 mg given intravenously. These high dose regimens for patients with spinal cord compression require fuller evaluation.

No response was seen in the 6 patients with symptoms arising from a retroperitoneal tumour who were treated with prednisolone. The relatively poor

response of patients with airways obstruction may indicate that some of these patients had malignant infiltrating lung disease. None of the 3 patients who had radiologically obvious lymphangitis carcinomatosa responded to prednisolone. This emphasizes the fact that dyspnoea arising from this cause is one of the more difficult symptoms to manage in terminal cancer.

The incidence of side effects with the 2 drugs has to be carefully interpreted in the light of the difference in dosages used. In particular, the incidence of oedema, weight gain and dyspepsia was very similar. This suggests that if used in identical doses, these particular side effects would occur less frequently with dexamethasone than with prednisolone. This must be put to the test in a more formal way but the reduced tendency to cause oedema is consistent with the relative lack of mineralcorticoid activity of dexamethasone.

The highly significant relationship between corticosteroids and the use of nystatin emphasizes the importance of maintaining a high index of suspicion that non-specific symptoms such as dryness of the mouth or sore throat in a patient receiving corticoids may indicate early candidosis.

Conclusions

Corticosteroids are important in symptom control in advanced cancer. They are used in over half of the patients in Sir Michael Sobell House and overall they produce a good response in 4 out of ten patients. For certain conditions, such as nerve compression pain, there is a substantially higher response rate. Dexamethasone appears to have several advantages over the more commonly used prednisolone. It is as effective as prednisolone for all indications where a comparison could be made between the 2 drugs and there is some evidence that it may be more effective than prednisolone in the relief of pressure symptoms related to a tumour mass. The incidence of side effects with dexamethasone and prednisolone is broadly similar. There is a tendency for oral candidosis to occur more often with dexamethasone and a significant increase in the likelihood of psychological side effects and hyperactivity. However, these latter effects are relatively rare. In equivalent doses, it seems probable that dexamethasone is less likely to cause oedema, weight gain and dyspepsia.

Dexamethasone is much cheaper than soluble prednisolone (though not non-soluble prednisolone) and fewer tablets need be taken by the patient because of its greater potency.

On the basis of these results, we have adopted dexamethasone as our standard corticosteroid, whatever the indication. The only situation in which we now revert to soluble prednisolone is when a patient is unable to swallow tablets. We are currently carrying out an identical survey of the use of dexamethasone in patients with far-advanced cancer to see whether the expectations arising from this present study are borne out in practice.

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