USE OF METYROSINE IN THE ANAESTHETIC MANAGEMENT OF PATIENTS WITH CATECHOLAMINE-SECRETING TUMOURS

A case report

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SUMMARY

Metyrosine 1.5 g daily for 9 days decreased 24-h urine metanephrine concentration by about 60% in a patient with multiple catecholamine-secreting paragangliomas. Despite the considerable inhibition of catecholamine synthesis, this patient exhibited stress-induced sympathetic overactivity, indicated by increases in arterial pressure and serum catecholamine and urine metanephrine concentrations. It is concluded that metyrosine should be introduced early to the preoperative regimen. In this way, optimal inhibitory effect on catecholamine synthesis can be obtained and maintained for a sufficient time to allow catecholamine stores to become as close to normal as possible. Attainment of the optimal therapeutic effect is not clearly defined, but would seem to be best gauged by a combination of clinical tests of sympathetic responses and of suppression of urinary excretion of metanephrines or VMA.

The purpose of preoperative preparation of patients with catecholamine-secreting tumours is to protect them from the effects of an excess of catecholamines and to ensure a safe periorperative course. Adrenergic blocking drugs, such as phenoxybenzamine and propranolol, have been useful in reducing the effects of catecholamine excess before and during operation.

Another approach to the preoperative preparation of patients with catecholamine-secreting tumours would seem to be to decrease the rate of catecholamine synthesis with metyrosine (α-methyl-para tyrosine). This tyrosine analogue is an inhibitor of tyrosine hydroxylase, which catalyses the rate-limiting step in catecholamine synthesis, namely the conversion of tyrosine to dihydroxy phenylalanine (dopa). We report the use of metyrosine in the pre- and intra-operative management of a patient with multifocal catecholamine-secreting paragangliomas.

CASE REPORT

A 53-year-old white male developed labile hypertension in 1970. In 1977, he underwent investigation and functional cervical and abdominal paragangliomas were diagnosed. Subsequently, the abdominal paraganglioma was removed. The cervical paraganglioma was judged to be inoperable and was treated with radiotherapy. The 24-h urine metanephrine concentration remained increased at 5.5 mg/24 h (normal =< 1 mg/24 h), while the labile hypertension was partially controlled (140-150/90-110 mm Hg) with oral propranolol 20 mg and phenoxybenzamine 10 mg, three times daily.

Four years later, the patient was admitted to hospital for surgical correction of a right inguinal hernia. Labile hypertension was again noted, with marked increases of 24-h urine metanephrine concentrations (fig. 1). X-rays revealed a right rib abnormality and bone scan showed several rib and left femoral "hot spots". Subsequent rib biopsy demonstrated paraganglioma tissue. As the inguinal hernia interfered with walking, it was decided to proceed with surgery.

Oral propranolol 20 mg and phenoxybenzamine 10 mg four times daily were continued and, on the ninth day before surgery, oral metyrosine was added to the regimen. The dose was rapidly increased to 500 mg three times daily. Vital signs were observed closely and sequential 24-h urine samples were collected for metanephrine determinations (fig. 1). When good control of arterial pressure and a substantial decrease in urine metanephrine excretion were achieved, the patient was considered to be ready for surgery.
Premedication consisted of pethidine 75 mg and hydroxyzine 50 mg i.m. Two peripheral intravenous and a radial artery catheter were inserted.

On his arrival in the operating room, the patient's arterial pressure was increased (200–210/90–110 mmHg) and his pulse was 70–80 beat min⁻¹. Anaesthesia consisted of a continuous lumbar extradural block with 1.5% carbocaine (total volume, 28 ml). Throughout surgery the level of analgesia remained at T4–T10 and the patient was free of pain and discomfort. Sedation was accomplished with pethidine (total 40 mg i.v.). Arterial pressure remained increased and intermittent sodium nitroprusside infusion was required for its control. Total serum catecholamine concentrations were increased before and markedly during surgery (fig. 2). Urine metanephrine concentrations were also increased for 48 h after operation and then began to decrease (fig. 1). Arterial pressure changes during the period after operation generally followed the changes in urine metanephrines, which apparently reflected an excess of catecholamine release.

The patient had an uneventful postoperative course and was discharged with a continuing regimen of propranolol 20 mg and phenoxybenzamine 10 mg four times daily, and metyrosine 500 mg three times daily.

**DISCUSSION**

This report illustrates some of the problems encountered in patients with catecholamine-secreting tumours. It was evident at the time of the patient's admission that he had signs and symptoms of uncontrolled catecholamine excess. Indeed, 24-h urinary

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**Fig. 1.** Medication, arterial pressure and 24-h urine metanephrine concentrations before and during operation.
excretion of metanephrines was greater than noted previously (fig. 1), and the metastatic bone lesions (proved on biopsy) confirmed the likelihood of a recent growth or spread of the functional paragangliomas and indicated the need for more vigorous preoperative preparation. The clinical and laboratory data show that metyrosine provided the means to re-establish control in this patient.

The management of this patient is instructive regarding the attainment of optimal benefit from metyrosine. Despite a 50–60% decrease in urinary metanephrine excretion associated with significant improvement in arterial pressure control, clinical and laboratory evidence of stress-induced sympathetic overactivity was seen on two occasions (fig. 1). The first was related to the performance of a rib biopsy under local anesthesia. The second episode occurred on the day of surgery. These responses probably represent the effects of catecholamines released from tumor tissues and from peripheral stores.

Our experience indicates that attainment of normal or near normal arterial pressure, heart rate and urinary excretion of catecholamines or metanephrines, under relatively non-stressful conditions, is not a reliable predictive index of the subsequent intraoperative course. It remains to be determined if metyrosine at greater doses and maintained for longer periods would render normal the rate of catecholamine synthesis and prevent release of excess catecholamines during surgery.

A review of the literature indicates that, when used alone or in combination with adrenergic blockade, metyrosine is of value in protecting patients with catecholamine-secreting tumors from the deleterious effects of catecholamine excess (Sjoerdsma et al., 1965; Sjoerdsma et al., 1966; Jones et al., 1968; Bagnall, Salway and Jackson, 1976; Robinson et al., 1977; Hengstmann, Gugler and Dengler, 1979). One would expect that administration of metyrosine before operation should ensure a smoother course during surgery. However, available data do not permit a definitive conclusion (Sjoerdsma et al., 1966; Jones et al., 1968; Tcherdakoff et al., 1972; Bagnall, Salway and Jackson, 1976; Robinson et al., 1977; Bergman et al., 1978; Smith, Aukburg and Levitt, 1978; Hengstmann, Gugler and Dengler, 1979). As a result of our observations, we feel that different degrees of catecholamine synthesis suppression were achieved in the reported studies and this may account for the mixed clinical impressions reported. It is known that the degree of metyrosine inhibition of catecholamine synthesis is dose related and that there is variation in the amount required to achieve a given degree of inhibition (Sjoerdsma et al., 1965; Jones et al., 1968).

We believe that preoperative metyrosine should be introduced early so that the optimal effect can be obtained, usually in 7–10 days (Engelman, 1977) and maintained sufficiently long to achieve as much normalization of catecholamine stores as is possible. While the duration of this period cannot be predicted at present, it can be estimated from the data of Hengstmann and Dengler (1978) that, even with complete inhibition of excess catecholamine synthesis, normalization of catecholamine stores could take from 1 week to 50 days (four to five half-lives). More information is needed regarding the clinical and laboratory criteria most helpful in predicting the attainment of this goal, which presently would seem to be best gauged by a combination of clinical tests of sympathetic responses and the suppression of urinary excretion of metanephrines or VMA.
ACKNOWLEDGEMENTS

This work was supported in part by the General Clinical Research Center grant RR0645 to the Department of Medicine.

REFERENCES


USO DE METYROSINA EN LA GESTION ANESTESICA DE PACIENTES CON TUMORES QUE SEGREGAN CATECOLAMINA

SUMARIO

La administración de 1,5 gramos de metyrosina diarios por espacio de 9 días disminuyó en aproximadamente el 60% la concentración de metanefrina en la orina en un ciclo de 24 horas, en un paciente con paragangiomas múltiples que segregaban catecolamina. A pesar de la considerable inhibición de la síntesis de catecolamina, este paciente mostró una sobreactividad del sistema simpático inducida por la tensión, que se puso de manifiesto por un aumento de la presión arterial y por la concentración de catecolamina en el suero y en la de metanefrina en la orina. Se concluye que la metyrosina debe introducirse en el régimen preoperatorio en sus primeras fases. De esta forma pueden obtenerse y mantenerse los efectos inhibidores óptimos de la síntesis de la catecolamina durante el suficiente espacio de tiempo para permitir que el almacenamiento de ésta se acerque lo más posible a lo normal. La obtención del efecto terapéutico óptimo no está claramente definido, pero parece que se mediría mejor mediante una combinación de pruebas clínicas de las respuestas del sistema simpático y de supresión de metanefrinas en la excreción urinaria o de VMA.