Metoclopramide in the Diagnosis of Pheochromocytoma

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SUMMARY
Cardiovascular and plasma catecholamine responses to metoclopramide (MCP), a dopamine antagonist, were examined in 5 patients with pheochromocytoma, 12 patients with essential hypertension (EHT) and 9 normotensive (NT) subjects who displayed symptoms suggestive of pheochromocytoma on a constant daily intake of 100 mEq sodium and 80 mEq potassium. Significant pressor responses to intravenous doses of 5 mg of MCP, which produced no serious pressor episodes and no other undesirable side effects, were found only in the patients with pheochromocytoma, in contrast to the subjects with EHT and NT who tended to display slight depressor responses. After curative surgery for pheochromocytoma, the MCP-induced pressor effects returned to normal. Furthermore, the enhanced pressor effects of MCP in the patients with pheochromocytoma were associated with increased plasma norepinephrine (NE) concentrations. However, the plasma epinephrine (E) concentrations remained unchanged after the MCP injection. Thus, this dose of MCP appears to be a more suitable vasopressor provocative agent in the pharmacological diagnosis of pheochromocytoma compared to currently used agents.

Additional Indexing Words:
Blood pressure  Norepinephrine

PHEOCHROMOCYTOMA is usually suspected on the basis of a number of clinical findings, but only the biochemical assessment of excessive catecholamine production allows a certain diagnosis. Although measurements of catecholamines in the plasma and urine and their metabolites in the urine provide the most reliable means of diagnosing this disease,1,2 pharmacolog-
ical aids to diagnosis are also necessary for those patients who have normal or equivocal plasma catecholamine concentrations and when the proper evaluation of other possible causes of paroxysmal secondary hypertension is negative. Hitherto, two types of pharmacological aids—the vasopressor provocative test and the vasodepressor test—have been widely used. However, the usefulness of the vasopressor provocative tests remains limited because of the risk of hypertensive crisis and the relatively poor diagnostic specificity; accordingly, they should be performed only in experienced centers.

Recently, it has been shown that MCP, a dopamine antagonist which is frequently used in the treatment of gastrointestinal disorders, causes increases of blood pressure in patients with pheochromocytoma. Furthermore, some investigators suggest that this drug may induce dangerous increases in blood pressure in such patients.

In this paper, therefore, we assessed the usefulness, the specificity and the safety of this drug in diagnosing this disease. We found this test, involving the ability of MCP to elevate the blood pressure and plasma NE levels only in patients with pheochromocytoma, to be more safe, simple and specific than currently used provocative tests.

**Methods**

**Subjects:**

All studies were carried out according to the principles of the Declaration of Helsinki. Written permission to undertake the procedures was obtained from each subject after giving a detailed description and explanation of the protocols.

We studied 5 patients with pheochromocytoma, in 4 of whom the diagnosis was confirmed by surgical exploration. In the 1 patient who refused surgery the diagnosis was based on clinical and laboratory findings, including arteriography, computed tomography, glucagon provocative test and catecholamine levels in the adrenal vein (Table I). In the 4 patients who underwent surgery, the blood pressure and concentrations of plasma and urinary catecholamines returned to normal after removal of the tumor.

Nine NT subjects were strongly suspected of having pheochromocytoma because of anxiety, headache, palpitation and vasomotor lability. However, in none of these did the laboratory findings, including intravenous pyelograms and computed tomography, show any sign of pheochromocytoma.

Twelve patients with uncomplicated EHT, whose average blood pressure exceeded 140/90 mmHg when taken on 3 separate occasions, were also
used in this study. Secondary hypertension was excluded on the basis of the clinical features, routine blood examinations and radiological investigations and they were diagnosed as having mild or moderate EHT (WHO I or II). These patients were taken off all medications for more than 2 weeks prior to the study.

**Protocol:**

All studies were performed in a quiet, warm and well-lit room and under a 100 mEq sodium/80 mEq potassium diet. All subjects were fasted overnight, did not smoke, did not take tea or coffee and were kept supine during the study. An indwelling intravenous cannula was inserted in a forearm vein at least 30 min before the study was begun at 9:00 AM. After confirming a lack of pressor response to a 1 ml saline injection, each subject received an intravenous injection of 5 mg (1 ml) of MCP. Blood samples for assay of plasma catecholamines were obtained before and at 15 and 30 min after the MCP injection. For the plasma catecholamine determinations, the blood samples were collected in 5-ml prechilled glass tubes containing 5 mg ethylenediamine tetraacetic acid 2K. The samples were separated immediately by centrifugation and then stored at −20°C until assay. Arterial blood pressure and heart rate were recorded using an autophygmomanometer before and 1, 3, 4, 10, 15 and 30 min after the MCP injection. Basal levels of arterial blood pressure and heart rate were obtained by averaging 4 measurements done at 5-min intervals.

**Assay procedures:**

Plasma NE and E were determined by high-performance liquid chromatography and the trihydroxy-indole fluorometric method.\(^{15}\) The sensitivity of the plasma assay was 10 pg/ml. The inter- and intra-assay coefficients of variation were 5.5% and 2.6%, respectively, for NE and 11.1% and 4.4%, respectively, for E. The upper limit for plasma NE was 400 pg/ml and that
for plasma E was 100 pg/ml. All specimens were assayed within a week of sampling.

Statistical procedures:

Values were expressed as means±standard error. Statistical comparisons were made by Student’s t-test and analysis of variance with the modified t-test. In comparisons of catecholamines we employed non-parametric statistics (the Wilcoxon U test) because plasma catecholamines in EHT and pheochromocytoma cannot be assumed to conform to a normal distribution. The level of significance was set at p<0.05.

RESULTS

Intravenous injection of MCP caused no undesirable side effects in any of the subjects without pheochromocytoma. The only side effects which

Fig. 1. Changes in systolic (a) and diastolic (b) blood pressure after the administration of MCP (↓) in 3 groups. Bars indicate standard error. *p<0.05, **p<0.01; compared to the pretreatment values.
took place in 2 patients with pheochromocytoma were slight palpitations, and no dangerous hypertensive crisis was noted. Many of the subjects tested showed a tendency to sleep during the period of study, and all subjects were able to resume normal activity after the study.

*Cardiovascular responses to MCP:*

After MCP injection, both groups without pheochromocytoma revealed similar tendencies towards decreases in both blood pressure and heart rate (Figs. 1, 2). The patients with pheochromocytoma, however, showed a

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**Fig. 2.** Changes in heart rate after the administration of MCP (■) in 3 groups. Bars indicate standard error. **p<0.01; compared to results in the other 2 groups.

**Fig. 3.** Changes in blood pressure in each patient with pheochromocytoma after the administration of MCP (■).
significant elevation in both systolic and diastolic blood pressure at 3 min (Fig. 1). The changes in blood pressure in each patient with pheochromocytoma after the administration of MCP are shown in Fig. 3. This pressor response was transient and was not seen in subjects who received only vehicle. The heart rate in the patients with pheochromocytoma was also increased significantly compared to the results in the other 2 groups (Fig. 2). In addition, in the 3 patients with pheochromocytoma who underwent curative surgery, these MCP-induced pressor effects disappeared.

Changes in plasma NE after MCP:

Basal plasma NE values were 160±30 pg/ml (NT), 160±20 pg/ml (EHT) and 2300±1150 pg/ml (pheochromocytoma), respectively. All 21 subjects without pheochromocytoma had basal plasma NE values which were within the normal range. One of the 5 patients with pheochromocytoma had a basal plasma NE value which was within the range of the 21 subjects without pheochromocytoma (Table I).

The percent changes in plasma NE in the 3 groups after the administration of MCP are shown in Fig. 4. After the administration of intravenous MCP, the plasma NE was reduced in the subjects without pheochromocytoma at 15 and 30 min; the slightly elevated values in 4 of the 21 subjects at 15 min
were decreased to below basal values at 30 min. In contrast, at 15 min after the administration of MCP, the plasma NE value was significantly elevated in each patient with pheochromocytoma; more importantly, the plasma NE value in the 1 patient who revealed a normal value during the control period was elevated outside the upper limit for the 21 subjects without pheochromocytoma. Furthermore, at 30 min after the administration of MCP, the plasma NE values were further elevated in 2 of the 5 patients with pheochromocytoma; the reduced value at 30 min in 3 of the patients was significantly higher than the value for the control period. Moreover, the plasma NE values in the 4 patients with pheochromocytoma who underwent curative surgery did not respond to MCP post surgery.

Changes in plasma E after MCP:
Basal plasma E values were 37±6 pg/ml (NT), 33±5 pg/ml (EHT) and 250±190 pg/ml (pheochromocytoma), respectively. All 21 patients without pheochromocytoma had basal plasma E values which were within the normal range. Two of the patients with pheochromocytoma showed a basal plasma E value which fell outside the upper limit for normal persons (Table I). All subjects with or without pheochromocytoma demonstrated
lack of E response to the MCP injection (Fig. 5).

**DISCUSSION**

In the present study, both blood pressure (systolic and diastolic) and plasma NE rises following intravenous injection of 5 mg of MCP occurred only in patients with pheochromocytoma. No false-positive pressor and no NE-stimulating responses to MCP were noted in the patients without pheochromocytoma. All of the chemical and pharmacological tests for pheochromocytoma used widely at present occasionally yield false-negative or false-positive results. In our limited experience, however, the present test has provided excellent diagnostic specificity. This specificity was indicated by the rather opposite depressor and NE-suppressing response—although being expected with rest alone—to MCP in the EHT and NT subjects without pheochromocytoma and the disappearance of the MCP-induced pressor and NE-stimulating responses in the 4 operated patients following removal of their tumors. In addition, this test seems to cause few of the unwanted side effects encountered in currently used provocative tests. The only side effect noted by us was slight palpitation in 2 patients. In contrast, the other provocative tests, including the histamine,5) tyramine6) and glucagon7) tests, frequently give rise to undesirable side effects such as disastrous hypertensive crises, face flushes, intractable headaches, etc.

Recently, Bravo et al16) reported that the clonidine-suppression test was a useful adjunctive test for ruling out pheochromocytoma in hypertensive patients with suggestive symptoms and borderline catecholamine values. They stated that this suppression test represented a safe and simple technique involving the ability of clonidine to suppress plasma NE levels in normals by stimulating central α-adrenergic receptors.17),18) Although we recognize this suppression test as a useful aid in the diagnosis of pheochromocytoma, there are some advantages to our MCP test as compared to the clonidine-suppression test. Firstly, the clonidine-suppression test is based only on changes in plasma catecholamines values. Thus, in their study, both pheochromocytoma and EHT patients demonstrated similar reductions in blood pressure and heart rate. As they stated in their report, the lability of plasma catecholamines in response to emotional and physical stress would give rise to question. In our MCP test, the judgement is based on changes in both blood pressure and plasma NE values which show opposite responses in patients with and without pheochromocytoma. Since a blood pressure response is noted immediately after the MCP injection, we can immediately assess whether the patient has pheochromocytoma or not. Secondly, in the cloni-
dine-suppression test, the patients tested are required to lie down for more than 3 hours, whereas our MCP test is over within 30 min.

The mechanism of the enhanced MCP-induced pressor and NE-stimulated effect observed in our 5 patients with pheochromocytoma is unknown. However, recently Adler-Graschinsky et al\textsuperscript{19} have reported that MCP releases catecholamines directly or indirectly from a pheochromocytoma in vitro. Although the dose of MCP used in that study was large, it is reasonable to consider that NE was released directly from the pheochromocytoma by MCP in our patients.

While all of the present patients with pheochromocytoma responded to 5 mg of MCP in our study using Japanese, a lower dose of MCP might also be effective. If this is the case, we think this test could be even safe. Furthermore, we consider evaluation of changes in plasma catecholamines at 15 and 30 min after MCP useful for the purpose of enhancing the diagnostic value of our test. When MCP was administered according to this protocol, no serious pressor episodes occurred and only minimal discomfort in the form of palpitations was experienced in 2 patients. Even so, the immediate availability of phentolamine is recommended as a precaution.

We conclude that, based upon the results of our study, MCP appears to represent a suitable substitute for the vasopressor provocative agents currently used in the pharmacological diagnosis of this disease.

\textbf{References}


