The Use of Noscapine (Narcotine) as an Antitussive Agent*

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The pharmacologic effects of Noscapine† (Narcotine discovered by Rabiquet in 1817) have been studied for many years. Recently it has been demonstrated to be significant in preliminary clinical trials. Noscapine is the second most abundant alkaloid in opium, next to morphine. Its empirical formula is C2H3O2N.

Actually Noscapine bears little resemblance to the narcotic alkaloids, either chemically or pharmacologically. The structure of morphine, codeine, and similar compounds is based on a phenanthrene nucleus, whereas Noscapine is an isoquinoline derivative (related to papaverine). It is readily absorbed after oral or parenteral administration, disappears rapidly from the blood stream, and only traces appear in the urine. Its fate is unknown. It has been referred to as the least toxic of the opium alkaloids in mice, rats, and man. Up to 3 grams by mouth have been given to man with only minor side reactions. Chronic toxicity studies did not demonstrate any cumulative effects. No depressant action on respiration or the central nervous system has been observed up to toxic doses; stimulation may appear with higher doses. The effects of Noscapine on the gastrointestinal tract were insignificant. No effects on secretory activity and minimal effects on gastrointestinal movements were reported. Occasionally emesis and constipation were noted only with large doses. No significant analgesic action was observed. Potentiation of morphine analgesia with antagonism to side effects have been reported, but not definitely established. The parenteral use of Noscapine has been limited because of local pain. In experimental cough in animals and man, it was described as effective as codeine. No tolerance to the drug developed. Finally, although no antihistaminic action was found, it did inhibit the "allergic cough" in sensitized guinea pigs exposed to aerosols of specific antigen. It did not, however, prevent anaphylactic shock after injected antigen. In a study centering about the experimental production of cough in normal and asthmatic subjects, small doses of Narcotine (5 and 15 mg.) were demonstrated to have greater anti-
tussive activity (suppression of cough response to citric acid aerosols) than the 30 mg. codein.

Clinical Studies

Fifty-one patients with cough due to various types of pulmonary disease were placed on a program of Noscapine therapy in an attempt to evaluate its effectiveness as an antitussive agent. The vital statistics of each of these patients are summarized in Table I. The diagnoses included the following: acute bronchitis, allergic and non-allergic; tracheobronchitis; chronic bronchial asthma; chronic pulmonary emphysema; bronchiectasis; and pulmonary neoplasms.

In this group of patients, there were 27 women and 24 men, with ages ranging from 17 to 75 years. Most of them fell within the age range of 31 to 70 years. The duration of the cough varied from one week to 30 plus years.

The dosage of Noscapine varied according to the individual's needs for antitussive therapy. Seventeen received 15 to 30 mg. as a single bedtime dose. The remaining 34 received 15 to 60 mg. from two to six times daily. The relationship of dose to effect was graded from 0 to 4+ (Table II).

The overall results were graded from 0 to 4+ employing careful objective as well as subjective estimates of the degree of cough suppression (Table II).

<p>| TABLE II |
| NOSCAPINE (P.O.) |
| Relation of Dose to Effect | Grade of Response |</p>
<table>
<thead>
<tr>
<th>Dose (Mgm.) Time Adm.</th>
<th>Trials</th>
<th>0</th>
<th>1+</th>
<th>2+</th>
<th>3+</th>
<th>4+</th>
</tr>
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<tbody>
<tr>
<td>15 HS</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>15 BID</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 TID</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td>4</td>
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<tr>
<td>15 4ID</td>
<td>1</td>
<td></td>
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<td></td>
<td>1</td>
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<tr>
<td>30 HS</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>30 TID</td>
<td>4</td>
<td></td>
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<td>3</td>
<td>1</td>
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</tr>
<tr>
<td>30 4ID</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>30 6ID</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>60 4ID</td>
<td>10</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 6ID</td>
<td>2</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>3</td>
<td>5</td>
<td>20</td>
<td>19</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(9)</td>
<td>(37)</td>
<td>(35)</td>
<td>(13)%</td>
<td>Response</td>
</tr>
</tbody>
</table>

*Table I omitted because of length, will appear in reprints.
A comparison with other antitussive agents was attempted in 30 trials. This data appears in Table III. The side effects and loss of effectiveness are also recorded in Table IV.

**Discussion**

Fifty out of 54 trials with Noscapine in 51 patients revealed beneficial effects graded from 1+ to 4+. Thus the effectiveness of this antitussive agent was observed in 94 per cent of those treated. However, the most significant effects were observed in the group with 3 to 4+ suppression. This constitutes 26 trials out of the group—(48 per cent), (Table II).

A comparison of the relative effectiveness of Noscapine with dihydrocodeinone, X-71, codeine, dilaudid, and diphenhydramine-aminophyllin (hydryllin) revealed the following: Less effectiveness in seven of 30 trials; no further changes in nine of 30 trials; and significant improvement was noted with Noscapine over the other antitussive agents in 14 of 30 trials (Table III).

There were no side effects in 45 of those treated. However, drowsiness was noted in three, difficulty in raising secretions in two, and headache in one. A gradual loss of effectiveness was observed in three. The nature of this loss of effect could not be determined.

**CONCLUSIONS**

1. In clinical studies, Noscapine administered orally in doses of 15 to 60 mg. at graded intervals proved effective as an antitussive agent in 94 per cent of 54 trials in 51 patients who were treated for cough due to various types of bronchopulmonary disease. Its maximum effectiveness...
(3 to 4+ cough suppression), however, was noted in 48 per cent of the overall group.

2. In 23 out of 30 trials, (77 per cent), comparable or better effects were observed with Noscapine when compared with other antitussive agents.

3. There were no side effects noted in 45 persons treated with Noscapine. Moderate drowsiness was observed in three patients; difficulty in raising secretions in two; headache in one. A gradual loss of effectiveness was observed in three cases. No gastrointestinal complaints or respiratory depression was noted in any of the cases receiving Noscapine.

CONCLUSIONES

1. Según los estudios clínicos, la Noscapina por vía oral a la dosis de 25 a 60 miligramos con intervalos graduales, se mostró efectiva como agente béquico en el 94 por ciento en el grupo 51 enfermos en los que se hicieron 54 ensayos, entre enfermos de diversos padecimientos broncopulmonares.

La efectividad máxima sin embargo (3 a 4 + de supresión de tos), se notó en 48 por ciento del conjunto.

2. En 23 de 30 ensayos (77 por ciento) se observaron efectos comparables o mejores, de la Noscapina frente a otros agentes béquicos.

3. No hubo efectos colaterales en 45 personas tratadas con Noscapina. Moderada somnolencia en 3 enfermos; dificultad para expulsar las secreciones en dos, dolor de cabeza en uno. Se observó pérdida gradual de eficacia en tres. No hubo molestias gastrointestinales ni depresión respiratoria en ninguno de los casos estudiados.

RESUME

1. Au cours d'études cliniques, la "Noscapine"; administrée par la bouche aux doses de 15 à 60 mmgr. à intervalles également espacés, s'est montrée efficace, contre la toux imputable à différentes sortes d'affections bronchopulmonaires, dans 94% des 54 essais pratiqués chez 51 malades. Son maximum d'efficacité cependant, fut notée dans 48% du groupe total.

2. Dans 23 cas sur 30 essais (77%) des effets comparables ou meilleurs que ceux d'autres sédatifs de la toux furent observés avec la Noscapine.

3. On ne nota aucun effet secondaire chez 45 personnes traitées par la Noscapine. On observa un peu de somnolence chez trois malades; de la difficulté à expectorer chez deux; des maux de tête chez un malade. On nota dans trois cas une perte progressive de l'efficacité du produit. Il n'y eut de complications gastrointestinales ou de diminution de la fonction respiratoire dans aucun des cas traités.

SCHLUSSFOLGERUNGEN

1. Bei klinischen Versuchen erwies sich Noscapin bei oraler Zuführung in Mengen von 15-60 mg. in abgestuften Intervallen als ein wirksames hustenstillendes Mittel in 94% von 54 Proben an 51 Kranken, die in Behandlung standen wegen Husten als Folge verschiedener Typen von Bronchopulmonalen Erkrankungen. Seine maximale Wirksamkeit (3-4 +
Hustenunterdrückung) wurde in 48% der gesamten Gruppe beobachtet.
2. Unter 23 von 30 Prüfungen (77%) wurden vergleichbare oder bessere Wirkungen festgestellt mit Noscapin im Vergleich mit anderen hustenstillenden Mitteln.
3. An 45 mit Noscapin behandelten Personen wurden keine Nebenwirkungen bemerkt. Mäßige Schläfrigkeit machte sich bei 3 Kranken bemerkbar; Schwierigkeiten, das Sekret abzuhusten, bei 2 Kranken; Kopfweh in einem Fall. Ein allmählicher Verlust der Wirksamkeit wurde in 3 Fällen beobachtet. Es kam zu keinen gastrointestinalen Schwierigkeiten oder respiratorischer Schwächung bei irgend einem der mit Noscapin behandelten Fälle.

REFERENCES