Anti-Cholinergic Effects of Clomipramine (Anafranil)

D Thursfield, MB, ChB, DPM, Senior Psychiatric Registrar, Highcroft Hospital, Birmingham, England

The ability of Anafranil to generate unwanted side-effects of hyperhidrosis, constipation, glaucoma and dry mouth have been recognized since its introduction into clinical practice in the mid-1960's. In this paper, I have concerned myself with summarizing our present knowledge of the effects upon the autonomic nervous system, their frequency of occurrence and their relevance to clinical practice.

From both animal and human studies, Anafranil is thought to exert a direct inhibitory effect upon acetylcholine metabolism, rather than a competitive inhibition of acetylcholine at synaptic endings, resulting in blockage of both post-ganglionic cholinergic nerve endings (including the cholinergic innervation of sweat glands) an anti-muscarinic effect, and of autonomic ganglia, an anti-nicotinic effect, differing from other atropine-like drugs in this respect. Inhibition of cholinergic transmission results in (a) reduction of exocrine gland secretion, excluding milk (b) relaxation of smooth muscle in the gastro-intestinal and urinary tracts (c) mydriasis in the eye and (d) increased activity of eccrine sweat glands.

Frequency of side-effects
Beaumont & Seldrup (1972) in a study of 207 patients in general practice have highlighted the fact that many 'apparent' side-effects of Anafranil are not 'real' drug-effects but present before treatment commenced. Table 1 shows some of the more common anti-cholinergic side-effects and their incidence in both controlled and uncontrolled Anafranil trials, although in not all cases has the 'real/apparent' discrepancy been taken into account.

In general, side-effects are more frequent and incapacitating in the parenteral group. Several authors comment on the overall tolerance of these only if depressive or obsessional symptoms are being relieved.

Clinical aspects
Many of the effects listed in Table 1 appear within 24-48 hours of commencing treatment, regardless of the route of administration. In four trials (Carney 1969, Collins 1971, Kirikae et al 1969 and Jost 1969) authors comment on the lack of relationship between dosage and the number and severity of side-effects. Jacobides (1968) however, found in a series of fifty-nine patients, that increased dose correlated with a greater number of side-effects. Jost (1969) has suggested that the incidence of side-effects is determined by the pre-treatment level of autonomic activity.

Failure of anti-cholinergic effects to respond to a reduction in dosage can frequently be countered with cholinergic drugs without discontinuing therapy.

In comparison with other tricyclic antidepressants, Anafranil has been found to have fewer overall side-effects but a higher incidence of excessive sweating (Karkalas et al 1969).

1. Disorders of Salivation
Taking each side-effect individually in order of frequency of occurrence, dryness, bitterness
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</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>10</td>
<td>20–50</td>
<td>&gt; 50</td>
<td>&gt; 50</td>
<td>18</td>
<td>—</td>
<td>50</td>
<td>50</td>
<td>71</td>
<td>90</td>
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<tr>
<td>Sweating</td>
<td>11</td>
<td>10–20</td>
<td>21</td>
<td>75</td>
<td>14</td>
<td>27</td>
<td>30</td>
<td>47</td>
<td>25</td>
<td>87</td>
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<tr>
<td>Visual difficulties</td>
<td>5</td>
<td>—</td>
<td>1</td>
<td>8</td>
<td>6</td>
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<td>20</td>
<td>5</td>
<td>3</td>
<td>27</td>
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<td>Gastro-intestinal disorders</td>
<td>—</td>
<td>&lt; 2</td>
<td>9</td>
<td>15</td>
<td>2</td>
<td>14</td>
<td>12</td>
<td>7</td>
<td>6</td>
<td>61</td>
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<tr>
<td>Urinary difficulties</td>
<td>4</td>
<td>&lt; 5</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>59</td>
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O = Oral
P = Parenteral
and an unpleasant taste in the mouth are those most commonly encountered, and fortunately the least incapacitating, occurring in approximately 50% of patients. Many patients seek relief spontaneously by sucking acid sweets. The use of sialogogues in the form of Probanthine also have a place in relieving symptoms. There are no cases of sialitis or siaio-lithiasis reported in patients maintained on high doses of Anafranil over long periods of time.

2. Disorders of Sweat Gland Secretion
Mild to severe generalized hyperhidrosis occurring as a result of Anafranil therapy is rarely an indication for discontinuing treatment. Kirikae (1969) found two of twenty-two patients treated with Anafranil infusions with transient sweating, and four patients with persistent but tolerable symptoms. The use of anti-perspirants, astringents and sedatives is suggested when symptoms persist after reducing dosage.

3. Disorders of Vision
These include blurring of vision, teichopsiae, tunnel vision, ocular hypertension, and in association with the latter, precipitation of glaucoma in the predisposed (ie individuals with congenital narrowing or narrowing of the corneal angle with ageing). Anafranil's anti-cholinergic mydriatic effects, produces corneal angle closure, blocking aqueous drainage and increasing ocular hypertension, with resultant glaucoma.

Lowe (1966) and Riise (1969) stress the low risk of precipitating acute glaucoma using Anafranil, but recommend brief enquiry, before commencement of treatment, into previous attacks of blurred vision and nocturnal halo vision. Orou & Unterkircher (1970) examined fifty-two patients (ninety-nine eyes) with primary glaucoma receiving oral Anafranil 75 mg daily. No cases of ocular hypertension were reported. Kudo & Tsukiyama (1970) quote the case of a 35-year-old female patient developing persistent mydriasis with an absent light reflex for two weeks after discontinuing Anafranil therapy. In summary, glaucoma is not a contra-indication to the use of Anafranil but the appearance of halo vision and pain in the eye are indications for immediate ophthalmological opinion before continuing with treatment.

4. Disorders of Gastro-intestinal Motility
Symptoms include nausea, vomiting, constipation and diarrhoea. Nausea and vomiting are not uncommon in the early stages of intravenous therapy with Anafranil, and usually resolve with continued treatment or concurrent use of oral anti-emetics. Constipation occurs in 10–15% of patients and is well tolerated by most. Pélicier (1969) recommends high fluid intake with the judicious use of laxatives as a matter of routine in treating his patients with Anafranil. Diarrhoea as a direct anti-cholinergic side-effect is uncommon but responds to dose reduction or anti-diarrhoeal preparations. There are no reported cases of paralytic ileus in patients receiving Anafranil to date. It is noted also that ileostomy patients do not benefit from Anafranil therapy in producing less frequent bowel movements.

5. Disorders of Micturition
Frequency of micturition, dysuria, strangury and acute retention of urine have been described following the use of Anafranil. Cholinergic blockade results in relaxation of detrusor muscle, and inhibition of relaxation of the internal sphincter and trigone of the bladder. Dickhaut & Galiatsatos (1968) describe six patients presenting with acute retention of urine in 138 patients treated by intravenous therapy. One responded to dose reduction, two cases by discontinuing treatment and three cases using a cholinergic anti-spasmodic drug. Most authors regard the presence of a neuropathetic bladder, associated with diabetes mellitus and conditions resulting in prostatic hypertrophy to be an absolute contra-indication to the use of clomipramine.

Clinical significance of Anafranil side-effects
In looking at the anti-cholinergic effects of Anafranil, the question arises as to the possibility of making predictions from their appearance, severity or intolerance regarding response to treatment. Beaumont & Seldrup (1972) in their recent paper, comment that those patients who tolerate side-effects do so because of the effective anti-depressant
therapy of Anafranil in creating a sense of well-being early in treatment. In their study of 207 patients receiving oral Anafranil, it was noted that the forty patients who dropped out of the trial because of intolerable side-effects, also failed to show any clinical improvement.

Defining this population of non-responders would be of value to the clinician enabling him to provide more suitable treatment more effectively.

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