adherence of the placenta. Previous post-partum haemorrhage should be an indication for hospital confinement.

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ECOLID: A NEW HYPOTENSIVE AGENT

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During the past five years ganglion-blocking agents have been used extensively in the treatment of arterial hypertension. The discovery of the activity of hexamethonium by Paton and Zaimis (1949) placed at our disposal an active therapeutic agent capable of producing a substantial reduction in the blood pressure. Subsequent research has been directed to the synthesis of new drugs offering advantages over hexamethonium.

In the treatment of hypertension, it is desirable to obtain a sustained fall in the blood pressure by the oral administration of a drug producing a minimum of side-effects. Hexamethonium is inconstant in action by mouth, its duration of action is short, and it produces side-effects characteristic of generalized ganglionic blockade. Maxwell and Campbell (1953) examined a number of methonium homologues and indicated the suitability of one of them, pentolinium, for therapeutic application. At present pentolinium is the most active hypotensive drug available and it has been widely employed. Trapold *et al.* (1955) have described the pharmacological actions of a new synthetic compound, "ecolid" (SU-3088), and Grimson *et al.* (1955) have demonstrated its activity in lowering the blood pressure in man.

Trapold *et al.* (1955) have described a series of halogenated isoindolines with potent ganglion-blocking activity of long duration. Ecolid was the most active compound investigated. It is 4,5,6,7-tetrachloro-2-(2-dimethyl-aminoethyl)-isoindoline dimethochloride, the structural formula being as follows:

The chloride salt contains 83.45% active cation. In animal experiments it was found that this new compound is several times as active in parenteral dosage as hexamethonium, and twice as active as pentolinium. In oral dosage its activity is the same as pentolinium, but the duration of action is appreciably longer. Vagal activity is affected less than sympathetic. The relative shortness of the methylene chain is of interest. This suggests that the overall molecular length is of greater importance in obtaining a specific synaptic fit than the spacing between the quaternary nitrogen atoms.

Clinical Investigation

Twelve patients were selected who had severe hypertension and whose blood pressures remained high, despite admission to hospital and treatment by bed rest, sedation, and dietary and salt restriction. Five of these patients (Cases 1-5) had been treated previously with various ganglion-blocking agents for several years, and their readmission to hospital was considered necessary owing to the recurrence of hypertension during out-patient treatment. All the patients were investigated fully as described by Graham and Maxwell (1954). This series of patients formed a good test for a new ganglion-blocking agent, as the hypertension was severe in every case.

Ecolid was administered by mouth before breakfast, to facilitate absorption. During 85 observations it was found that the effective dose varied from 25 to 200 mg. In common with other ganglion-blocking agents, the response to the first dose was greater than that obtained subsequently, and higher dosage was required in those cases previously treated with sympathicolitics. In some cases a response was not obtained until the second or third day of treatment, suggesting a cumulative effect. A marked fall in blood pressure sometimes followed the initial dose of 25 mg. In every case adequate dosage produced a fall in blood pressure to the basal level, with increased peripheral blood flow as shown by a rise in temperature of the extremities, and postural hypotension. Evidence of vagal inhibition was present in the form of mydriasis, paralysis of accommodation, and dryness of the skin and mouth. Five barium examinations showed a variable depression of gastro-intestinal motility, this being marked after doses of over 150 mg. Postural syncope resembled that produced by pentolinium, loss of consciousness being slow and accompanied by nausea. The dose required to produce a marked fall in blood pressure was rather less than that of pentolinium, and the duration of action was approximately double. These results are compared with those from hexamethonium in the Chart.

Effect upon the blood pressure of single oral doses: mean of 50 observations upon each drug. C6=hexamethonium 250 mg.; 2050=pentolinium 100 mg.; SU-3088=ecolid 64 mg. Dosage in cation.

During the last four months ecolid has been used in the treatment of this series of 12 patients. It was found possible to lower the blood pressure to a satisfactory level in every case. The severity of the side-effects depended to some extent upon the dosage used. Mydriasis was a constant finding, and blurring of vision commonly occurred during initial treatment, but was less severe with maintenance dosage. Precautions were necessary to overcome development of constipation, and in three cases treatment had to be stopped owing to nausea and vomiting and obdurate constipation. A preference for pentolinium was expressed by two patients (Cases 2 and 5) who have had extensive experience of ganglion-blocking agents.

Bain *et al.* (1955) have shown that combination of reserpine with pentolinium enabled reduction in dosage of the latter and thereby a decrease in side-actions. Combined dosage of reserpine and ecolid was used in the maintenance treatment of Cases 7-12, reserpine, 2 mg. by mouth, being

given in the evening. Reduction in the maintenance dosage of ecolid was possible and side-effects were fewer. During the period of observation, tolerance to ecolid has not developed, and in some cases reduction of dosage has been possible. The response was good in eight cases and fair in one, the drug being stopped in the remaining three owing to severity of side-actions. These results are summarized in the Table.

Summary of Results of Treatment of 12 Patients with Severe Hypertension. Mean Blood Pressures when Recumbent are Recorded. Patients 7-12 Received Also 2 mg. Reserpine by Mouth at Night

Case No.	Sex and Age	Type of Hypertension	B.P. Before Treatment	B.P. During Treatment	Daily Dose of Ecolid	Side-effects	Result
1	F 38	Malignant	260/155	150/100	175 mg. b.d.	Unable to read. Slight dryness of mouth	Good
2	F 38	Malignant (toxaemia of pregnancy 3 years ago)	260/140	180/100	150 mg. b.d.	Blurring of vision. Moderate constipation	"
3	M 41	Malignant	240/140	150/100	150 mg.	Blurring of vision. Severe constipation	Drug withdrawn
4	M 44	Malignant (acute nephritis 24 years ago)	250/140	145/100	200 "	Unable to read. Dryness of mouth and dry cough. Slight constipation	Fair
5	F 57	Essential, malignant phase	230/140	165/105	75 "	Nausea and vomiting. Constipation. Light-headedness	Drug withdrawn
6	M 53	Malignant	210/120	160/90	100 "	Blurring of vision	Good
7	F 57	Essential	215/150	150/95	75 mg. b.d.	Blurring of vision. Slight dryness of mouth	"
8	M 61	"	220/110	140/85	50 mg.	Slight dryness of mouth	"
9	F 64	"	220/120	160/70	25 "	Severe nausea and vomiting. Constipation	Drug withdrawn
10	F 57	"	240/150	140/95	125 mg. b.d.	Slight dryness of mouth	Good
11	F 55	"	220/140	135/90	125 mg. b.d.	Nil	"
12	M 59	Essential, malignant phase	180/120	155/95	100 mg.	Blurring of vision	"

Discussion

The introduction of ganglion-blocking agents in the treatment of hypertension is due to the work of Dale (1914), who described the properties of tetraethylammonium (T.E.A.). Recognizing the improvement which could be obtained by surgical procedures in patients with severe hypertension, Lyons *et al.* (1947) employed T.E.A. to reproduce the effect of sympathectomy. The need for such a drug was demonstrated by the extensive use of T.E.A. in intravenous dosage, despite its marked toxicity. Organe *et al.* (1949) showed that the bis-quaternary amine hexamethonium was a practical method of lowering the blood pressure. However, the generalized activity of this drug proved to be a handicap, as its actions, beyond inhibition of sympathetic ganglia, constituted side-effects. The serious complication of ileus, due to vagal block, has been described. Paton (1951) suggested that it might be possible to produce ganglion-blocking agents more or less adapted to different ganglionic systems. It was with this purpose that Maxwell and Campbell (1953) investigated a large number of new drugs inhibiting synaptic transmission. Pentolinium was found active in lowering the blood pressure in smaller doses than hexamethonium, and it had only a weak action on gastric secretomotor activity. It is effective by mouth in a high proportion of cases, and it has been combined successfully in oral dosage with reserpine.

The research by Trapold *et al.* (1955) has been concerned mainly with the production of a ganglion-blocking agent consistently active by mouth. Ecolid has met this require-

ment and has also a longer duration of action than pentolinium. This increase in consistency and duration of oral action is accompanied by side-effects intermediate between those of hexamethonium and pentolinium. The treatment of our patients has been complicated by these side-effects. However, we have found that combined dosage of reserpine and ecolid by mouth affords a practical method for the treatment of hypertension, particularly in the smaller dosage required for the less severely ill patients, when side-effects are reduced.

Summary

A new hypotensive drug, ecolid, has been used in the treatment of severe hypertension. Consistent activity by mouth has been confirmed. The initial dose should not exceed 25 mg., and treatment consists of 25 to 200 mg. administered before breakfast, with a dose also during the evening, if required. It is more active than pentolinium, but side-effects are more severe; the duration of action is longer. The combination of oral dosage of ecolid and reserpine has been found useful in the treatment of hypertension.

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Medical Memoranda

Delayed Onset of Signs in Extradural Haemorrhage

Variations in the clinical picture resulting from extradural haemorrhage are common, but it is unusual for the development of signs of cerebral compression to be delayed for more than 24 hours after the receipt of injury. The compression, once initiated, is usually rapidly progressive, leading to death within 48 hours if unrelieved. In the following case, consciousness was never lost, the onset of clinical signs was insidious, and operation was not performed until six days after injury.

CASE REPORT

On September 1, 1954, a boy aged 12 was riding downhill on his bicycle when the brakes failed. To stop the bicycle he put a foot between the spokes of the front wheel and was thrown over the handlebars, striking the right side of his head and his right leg on the ground. He did not lose consciousness, but vomited three times.

On admission to hospital he was found to be alert and bright, with good recollection of events before and after the accident. There were bruises in the right temporal region and over the right shin. The left eye had been removed in infancy following an injury, but the pupillary reactions on the right side were brisk and the optic fundus was normal. There was considerable haemorrhage from the right ear, and radiography showed a fine vertical fracture of the squamous part of the temporal bone on the right side. The pulse rate was 64.

Next day, apart from a little headache, the boy was well and the bleeding from the ear had stopped. Two days later