Cholinergic Stimulation of Globus Pallidus in Man.* (24835)

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This report is concerned with effects of acetylcholine chloride, oxyphenonium bromide and sodium chloride injected into the region of globus pallidus of persons with Parkinson's disease.

Materials and methods. Eleven persons with varying degrees of Parkinsonism have been injected with cholinergic and anticholinergic drugs. Bilateral injections were done in 5 persons and unilateral in 6, 5 right and 1 left. Symptoms had been present from 3 to 30 years with increasing severity despite drug therapy. All antiparkinson medication was stopped prior to test period. The patient was alert and cooperative during injection periods, and numerous clinical tests were done but only 4 will be reported in detail. Motor strength in the hand was tested with bulb dynamometer (Geckeler type). Muscular rigidity was evaluated and observed by passively flexing and extending extremities at joints. Rapid alternating movements were tested in hand and fingers by having patient open and close the fingers as quickly as possible for 30 seconds. Differences in electrical resistance of skin over head, trunk and limbs were measured (A. R. Spartana Co. Model 2R Neuro-dermometer). Temperature of skin was recorded over same body areas with surface pyrometer (E. M. Rauh & Co., Inc.). A Cooper chemopallidectomy catheter without a balloon was placed into region of globus pallidus by free hand method. The position of tip of catheter was determined by measurement on the pneumoencephalogram. The ideal locus for the tip on lateral x-ray was 10 mm below and behind anterior lip of the Foramen of Monro, and on anteroposterior x-ray 15-20 mm lateral from midpoint of third ventricle. This would place the point of injection at medial third of globus pallidus. The catheter was securely anchored to scalp, and its position checked by x-ray before and after each injection period. Injection lasted 7-10 days, with average of 3 injections spaced several days apart. Acetylcholine chloride (Merck) in 10% solution and oxyphenonium bromide (Antrenyl, Ciba) in 0.2% solution were the drugs studied. Sterile isotonic saline and 5% sodium chloride were used as control injections. The drugs were dissolved in sterile isotonic saline at time of injection. Total amount of fluid injected was 1 ml and rate of injection was constant at 0.05 ml/minute. The patient sat up during injection to prevent regurgitation of fluid along catheter track.

Results. A total of 88 injections has been done, 56 with acetylcholine chloride, 16 oxyphenonium bromide, 15 isotonic saline, and 1 with 5% saline. The events reported with each drug did not necessarily occur following every injection but represent a composite of observations.

Isotonic saline and 5% saline solution resulted in no clinical change.

Acetylcholine chloride. During initial 5-10 minutes of injection, a stimulatory effect occurred with increase in amplitude of tremor in the contralateral arm or onset of focal seizure in the contralateral face. Conjugate deviation of eyes or turning of head away from injected side was noted. Increase in tremor was most often unilateral, but in one man the tremor increased in both arms, but more so in the contralateral extremity. Increase in tremor lasted only a minute or 2 while focal twitches or adversive eye movements might continue several hours. The lower extremity was not involved in this increased activity even though tremor and rigidity were present. During this period the patient was conscious. Rigidity and tremor were reduced after initial excitatory stage; the patient would exclaim about looseness of the contralateral upper limb. The arm was most often involved with less noticeable effect in the leg. An increase in rapid alternating movements and range of movement accompanied this decrease in rigidity. Reduction was most pronounced in forearm, wrist and fingers. Loss of rigidity occurred in

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some instances without any motor weakness. Following a single injection, rigidity decreased for several hours to days. Hoffman or Babinski sign was noted in several persons within a few minutes of injection. The reflex change was not necessarily found in the extremity with reduction of rigidity or tremor. The reflex change lasted several hours or a few days when it disappeared but would then reappear with repeat injection. Parasympathetic stimulation occurred at time of injection with increased sweating in contralateral arm or leg, and a rise in skin temperature. Nausea and vomiting occurred in only a few instances, for a short time. Two persons became unresponsive during the first few minutes of injection. This was not associated with fall in blood pressure but there was a drenching sweat, and one person developed extrasystoles. Within 5 minutes both were awake and normal. Blood pressure, pulse and respirations rarely changed during injection.

Oxyphenonium bromide. Rigidity was reduced in 5 instances, tremor in 2, with no change in motor power. The sudoresis on opposite side of body produced by intracerebral acetylcholine was blocked by intracerebral injection of oxyphenonium bromide. A central facial paresis was noted after 1 injection, a Babinski reflex once. One man had difficulty opening his eyes after injection. One man became sleepy and exclaimed that his head had gone to sleep. Nausea and vomiting did not occur. Several persons complained of dryness of mouth 15-30 minutes after injection, and a blotchy erythema occurred in one man.

Discussion. Cushing(1) demonstrated parasympathetic stimulation of the hypothalamus by intraventricular injections of pilocarpine in man. Henderson(2) produced similar parasympathetic responses following intraventricular injections of acetylcholine and eserine. Our report indicates that parasympathetic effects may occur on contralateral half of body after injection of a cholinergic drug into the region of globus pallidus. The site of this stimulation is not certain as diffusion into the adjacent internal capsule and/or hypothalamus may occur. It is possible to block this response by intracerebral injection of oxyphenonium bromide into the same region. Electrical and mechanical stimulation of the lateral wall of 3rd ventricle in man(3) and animals(4) may result in altered consciousness and cardiac arrhythmia. Two patients reported here had an intense parasympathetic response, unconsciousness and cardiac arrhythmia, suggesting chemical stimulation of the hypothalamus.

The mechanism of drug action on rigidity and tremor is not clear from these observations. Alterations in vascularity in the injected region may be responsible. A purely mechanical effect caused by injecting a fluid seems unlikely in view of negative results with saline injections. Concentration of acetylcholine was high, and it is well known that changes in concentration of a drug may result in excitatory or depressive effects. It is possible that high concentration resulted in a block of nervous activity in the region of globus pallidus. Bailey(5) has demonstrated a blocking effect of procaine hydrochloride in frontal lobes of man, and Narabayshi(6) postulated the blocking effect of procaine in the globus pallidus as responsible for reduction of tremor and rigidity in his cases of Parkinsonism.

Summary. A 10% solution of acetylcholine chloride injected into the globus pallidus of persons with Parkinsonism resulted in initial excitatory stage with increase in tremor and parasympathetic activation. Parasympathetic response was blocked by intracerebral injection of an anticholinergic drug, oxyphenonium bromide. The exact mechanism of drug action is not known, although cholinergic sensitive regions appear to exist in or near the globus pallidus.

1. Cushing, H., *Proc. Nat. Acad. Sc.,* 1931, v17, 163, 239.

2. Henderson, W. R., Wilson, W. C., *Quart. J. Exp. Physiol.,* 1936, v26, 83.

3. White, J. C., *Res. Pub. Assn. Nerv. Ment. Dis.,* 1940, vXX, 854.

4. Beattie, J., Brow, G. R., Long, C. N. H., *Proc. Roy. Soc. London*—Series B., 1930, v106, 273.

5. Bailey, O. T., *J. Neurosurg.,* 1952, v9, 21.

6. Narabayshi, H., Okuma, T., Shikiba, S., *AMA Arch. Neurol. and Psych.,* 1956, v75, 36.

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