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- LARGACTIL -

SOME PRELIMINARY CLINICAL OBSERVATIONS

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In April 1952 a report, by two anaesthesists Drs. F. Hudon and A. Jacques (1), (2) of the Department of Anaesthesia, Hotel-Dieu Hospital Quebec, presented a new drug Largactil (Chlorpromazine) which was employed in Anaesthesia to (1) stabilise the neuro-vegetative system, (2) reduce surgical stress, (3) create a state of indifference in the patient, (4) decrease the quantity of anaesthesia and sedatives normally required, (5) abolish post-operative nausea and vomiting.

Chemically, Largactil is a derivitive of Phenothiazine -

and is closely related to Diparcol and Parsitan (anti-parkinsonian agents) and Phenergan (antihistiminic agent with central and autonomic

nervous depressant activity).

It is described by Poulenc (3) as follows: "Largactil possesses multiple pharmacological properties which principally derive from its 'neuroplegic' action on the autonomic and central nervous system, it is vagolytic and sympathicolytic, it potentiates the activity of a number of centrally acting drugs".

A preliminary investigation with this drug, one in which this writer was permitted to participate, on medical and surgical cases provided some very interesting results. Of particular interest to this paper was the evidence presented for the possible location of its neuroplegic action.

It is known that a high spinal block up to T.1 without a pressor drug a complete blockade of the sympathetic system is obtained leaving the autonomic system in control of the parasympathetic, resulting in a lowered blood pressure and slow pulse, a state which is often of great surgical value. In order to achieve this state, however, the patient must be asleep prior to administration and kept asleep throughout. When the patient is asleep central defenses do not occur which would tend to raise the blood pressure. Cortex surpressing anaesthetics are generally employed to keep the patient asleep. When Largactil (50 mg) was used instead of the usual cortex surpressents the same effects were noted, namely, the central defenses were effectively counteracted. From previous observations it is known that Largactil does nor primarily affect the cortex because the patient under its influence does not actually sleep.

The foregoing observations suggest that Largactil blocks at a higher level than either hexamethonium salts or spinal anaesthesia but not at the level of the cortical anaesthesias. This would lead one to believe that Largactil effects some intermediary level. The results so far observed has led this writer to postulate that Largactil must act in the diencephalon inhibiting the "vegetative center", which according to Cobbs (b) integrates the autonomic and somatic reactions.

If Largactil is given first and a pressor drug is added, little appears to happen. Certainly pressor drugs do not have the normal effects seen when used to counteract a spinal block or a block resulting from a hexamethonium salt. We have tried this a number of times and could not convice ourselves that it took effect. However, animal experiments show that adrenaline, nor-adrenaline and possibly methedrine raise the blood pressure. Slight peripheral vasoconstriction with a rise of blood pressure occurs with pituitrin or ergotrate in the presence of Largactil. From a clinical point of view there does not appear to be a true antidote for Largactil. But do we need an antidote? If our hypothesis is correct, that Largactil depresses the diencephalon, and thus stabilises the organism in a state of hibernation in which vegetative functions are not disturbed by peripheral or cortical stimuli, we do not! This would also be the explanation for the observation that Largactil has a low activity on parasympathetically-mediated functions and a high anti-adrenergic activity because parasympathetic activity is believed to have primarily the function of control whereas the sympathetic function is designed "to act as a whole as an emergency mechanism". (Cobb) (L)

Clinical impressions would appear to be in favour of this view. After using this drug for 6 months we came to the conclusion that Largactil is quite safe without an antidote as we have had no difficulties with it and it has been lifesaving in a number of desperate situations. To be safe with this drug one main thing to be remembered is the fact that a fall of blood pressure might occur by what appears to be centrally caused vasodilatation. The distribution of bllod therefore is determined mainly by gravity. Should there be any danger of anoxemia, the patients head should be lowered and the feet raised. As long as the patient lies flat or is in a slight Trendelenburg position the vital centers have enough blood, no cerebral anoxemia will ensue and he is safe. We have encountered no real problem relative to severe postural hypotension, and most patients develop tolerance to any orthostatic effect after a day or two of continuous treatment, probably because they reached a new level of homeostasis.

Largactil further is said to have sedative properties and to potentiate sedatives and analgesics. Its own sedative properties are questionalbe, usually patients do not sleep with it but they rest comfortably, are disinterested and indifferent. Pain does not matter any longer although it still is present, as a patient with a second and very severe coronary thrombosis most convincingly stated. We feel that Largactil potentiates other drugs in this manner. If one is already indifferent to his pain, it does not need much analgesic to take it away, if one is already resting it only needs little sedative to put the cortex asleep. If the neurophysiological conception is correct that there is a wakefulness center in the hypothalamus and Largactil supresses the diencephalon, these findings can be understood.

Thus far, things were reasoned out by observing the drug's action in a multitude of conditions and when we received some of the French literature on Largactil it pointed in the same direction. In one article from Paris, France, on neurotoxicoses in infantile diarrhea and encephalitis, Sorel (5) and others state that those neurotoxicoses are the result of a defensive over-reaction of the diencephalon against this agression. They maintain also that Largactil anesthetizes these centers, therefore gaining just enough time to catch up with dehydration and electrolyte imbalance and to combat infection. They are certain that they were able to save a number of children in whom they otherwise would not have had the time to reverse the process of defensive overreaction of the diencephalon. Nature's defense mechanisms are built for transient emergencies and may prove dangerous in themselves when needed too long. In a good many cases breaking the defense, might give the necessary time to catch up with the cause.

The observations we have seen agree in principle with Sigmand and Bouttier (6) who coined the term psychoplegic. They also believe that Largactil acts on the diencephalon interrupting its functions and those of the cortex. They are of the opinion that it is not an analgesic.

The unusual pharmacological properties of this drug when used as a adjuvant to anaethesia and other effects observed during the course of this preliminary investigation as well as evidence provided in the literature by others experimenting with the clinical use of Largactil immediately suggests its possible usefulness in the field of psychiatry. This impression has been further substantiated in a recent article by Lehmann and Hanrahan.

An opportunity for using Largactil in a psychiatric setting presented itself during this writer's residence at the Ontario Hospital, London. Our psychiatric experiences with Largactil in London were limited by the fact that we did not have large amounts of the drug available and also that we had only a limited range and number of patients where the effects of this drug would possibly be of value. It was decided, however, to try Largactil in patients who were either acutely disturbed or in whom anxiety and tension were major features. The following cases demonstrate the methods used and the results obtained.

Case 1

A 59 year old widow who had had a manic attack 25 years previously was suffering from an agitated depression. The patient had been violent and completely incoherent at home, and on admission she had a respiratory rate of 12 per minute from sedation. She showed marked dehydration and high temperature. Hence H M A did not seem to be a good drug to use. Sodium Amytol i.m. depressed her respiration to 15 per min. did not hold her mentally, and we had to resort to tube feeding. At this point ECT would usually have been employed. However, it has often been stated that in a very tense and anxious patient ECT may increase tension. We could affirm Kretschmer (8), findings with prostigmin that ECT often achieves better results when there is less vegetative disturbance. Therefore, as we wished to control her dehydration, which is a severe stressor in itself, before she was started on ECT, Largactil was tried and the patient received 4 doses of 50 mg. i.v. over a 48 hour period. The results were impressive.

The patient became quiet and cooperative, she ate and drank readily and her temperature was lowered. Her delusional self accusations were no longer so predominant although clearly present. Quite a normal conversation could be maintained as long as it stayed in the past or concerned the weather. We then gave ECT which we believe remained the treatment of choice. After the first treatment the patient was very tense and anxious, complaining about pressure in her head and believing, that this treatment would do her more harm than good.

After the second ECT the patient received 50 mg. Largactil i.m. with the result that she dozed off for the rest of the afternoon. The next morning she could remember only going over to the other building. She was calm and felt very well. The same effect could be achieved in subsequent treatments using only 25 mg. i.m. To convince myself I gave the fifth ECT without Largactil when the patient was much improved and when I was less afraid of her again becoming tense. On this occasion the patient felt miserable that afternoon and the next day, and complained loudly about that one terrible treatment. She readily agreed that she liked ECT better with a needle afterwards since it made her forget the treatment.

I believe that this patient had a smoother and more pleasant course with much less complaint than usual, and anxiety regarding treatment was greatly diminshed. Largactil is the only drug we have encountered that effectively does away with post ECT complaint.

Case 2

Another female, with agitated depression needed 150 mg. Largactil i.m. daily combined with sodium amytal per os gr. 1. t.i.d. and gr. lll h.s. to prevent her from picking her skin which showed bleeding and partially scarred lesions. Within 3 days of this treatment her skin had healed. Largactil orally with the same amount of barbiturates did not prevent her from picking her skin, and not before she had her 3rd ECT with Largactil afterwards did she more or less abandon this habit. We have found in other cases as well that Largactil parenterally is far superior to oral administration.

Case 3

A 33 year old female immigrant became psychotic shortly after she gave birth to an illegitimate child. She had delusions of having given birth to a dog, heard references to herself on the radio, thought the government was against her, and was diagnosed as a paranoid schizophrenic. After she had been 4 weeks in the hospital she became acutely disturbed when she saw her child and after she had been told that her mother had suddenly died. She was secluded and refused nourishment. She had been receiving ECT which did not control the excitement at all and needed 2 HMA's a day. One Sunday at 2 p.m. we gave her 50 mg. Largactil i.m. with astonishing results. It took her about one hour to quieten down, she rested the afternoon and at 6:30 p.m. the ward called me to report that the patient was well oriented, had gone to the bathroom, got dressed and commented on her appearance, that she had eaten and drank and seemed to have "snapped out of it".

She received another injection the next day and 2 ECT on the following days, but again became disturbed and relapsed to her previous state and was again secluded. She was then placed on a three day schedule with 25 mg. Largactil i.m., t.i.d. supplemented by sodium amytal gr. 111 h.s. After this she had a lucid internal, wrote home that she had suddenly awakened in a mental institution. She was eager for explanation and would hardly believe her previous delusions but could understand that they must have been signs of a mental illness. We then gave her Largactil per os which did not hold her and within 3 days she was again secluded but at least did not stop eating. At this point ECT was increased and the patient received 2 treatments for 2 days and 3 more during the following 5 days. After this we could take her out of seclusion but she was confused, completely disoriented, believed she was at a neighbours in her homeland, talked in her childhood dialect, was refractary to explanations. It took 10 days for this organic syndrome to clear up. The patient again became as disturbed as she had been previously, voicing delusions of having killed her parents, and of having been with a dog. Three days of Largactil 25 mg. i.m. t.i.d. brought about another clear state. She wrote a very sensible letter, denied her previous delusions, recognised her hallucinations as untrue and dismissed them, was nicely dressed and concerned about her future. We could maintain her on Largactil parenterally and we continued Largactil for 4 more weeks. ECT brought about a very good remission.

A number of chronic anxiety states, one with an acute crisis in which she had raised her blood pressure well above the scale of the sphygmomanometer, could be put on maintenance doses

of 4 tablets a day, (100 mg.), after they had been treated parenterally for some days with daily doses of up to 150 mg.

In some cases that could not be helped by routine measures, we placed the patient on a maintenance dose of Largactil. This latter group included psychosis associated with arteriosclerosis. Largactil has been lifesaving in a woman over 80 with marked arteriosclerosis who had an 18 month history of cardiac fibrillation and an embolus high up in her femoral artery. Also an acutely disturbed patient aged 76 with arteriosclerosis and a 81 year old depressed patient were established on 4 tablets daily, and did well. This has lead us to believe that Largactil may be used in the aged with comparative safety.

Side effects and toxicity

Our experience gave no indication of toxicity. There was one case of intolerance observed. The patient became jittery under treatment. No alcoholics or drug addicts were treated and it must be remembered that Largactil potentiates ethyl alcohol and barbiturates and should not be used in ethylic or barbituric coma. However, it should be a valuable drug for use in withdrawal symptoms. Largactil should also be used cautiously in those patients suspected liver damage (7). There is usually a fall in blood pressure under parenteral administration and the patient should be supine for at least one half hour after an i.m. injection. This effect is more apparent at the start of treatment, and is usually accomodated by the second or third day.

Conclusions

Our studies to date have led to the following tentative conclusions:

1. Largactil acts as a vegetative stabilizer apparently by inhibiting the diencephalon and thus the central pathways for which the diencephalon is a relay station and thereby creating what has been described as a "psychoplegic" action, i.e. reduction in anxiety while consciousness remains clear thereby facilitating psychotherapeutic contact.

2. It is safe as long as the following possibilities are remembered:

   (a) An orthostatic fall in blood pressure

   (b) Liver disfunction on high and prolonged dosage

   (c) Potentializing effect on barbiturate and alcohol

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