PRELIMINARY REPORT ON THE TREATMENT OF MENTALLY DISORDERED PATIENTS BY INTRATHECALLY ADMINISTERED PHENOTHIAZINE DRUGS AND AN ANTISEROTONIN SUBSTANCE

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PART I. THE USE OF PHENOTHIAZINES INTRATHECALLY

The effectiveness of the phenothiazine group of drugs in the treatment of certain forms of mental disease has now been established after several years of use. But, although the treatment is effective, in certain cases it still takes 4 - 5 months before a patient can be discharged from hospital. It has been the experience at Weskoppies Hospital, Pretoria, that the treatment of catatonic schizophrenics usually takes up to 5 months. After 5 or more electroconvulsive treatments, followed by oral doses of trifluoperazine, it took about 18 - 20 weeks before they were apsychotic and ready for discharge.

This raised the question whether this period could be shortened and a quicker response obtained. One possible method that suggested itself was the intrathecal injection of one of the phenothiazines. The reasoning behind this was as follows:

1. Lups and Haan[1] in their book *Cerebrospinal Fluid* have shown that the permeability of the blood-brain barrier is markedly decreased in schizophrenics.

2. A study,[2] done in England, has shown that dyestuffs injected into the ventricles of experimental animals permeate through the brain matter to the cortex.

3. Experimental work[3] (done at the Radiotherapy Department of the Pretoria General Hospital) has shown, by doing radioisotope tracer studies, that radioactively labelled human serum albumin and sodium injected intrathecally could be followed by the Geiger counter. It took the radioactive matter 40 minutes to reach the upper cervical area, and 100 minutes to be spread over the whole cranial area.

4. The dosage of phenothiazines used in psychotics differs markedly from the dosage used in mentally normal patients. The initial dosage of the phenothiazines in psychotics is usually very high and, as the condition improves, the dosage is slowly decreased, otherwise side-effects come to light.

The hypothesis was made that, if the above represented a true picture, it might be feasible to try to administer phenothiazine derivatives by the intrathecal route, thereby

perhaps circumventing the blood-brain barrier's relative impermeability, and thus possibly shortening the duration of treatment.

Some support for this view was found in the fact that it had been shown that intrathecal injections of methylprednisolone acetate (40 mg. every 2 weeks) had the same effect on multiple sclerosis as large oral doses (750 mg. daily for adults).[4] This finding strengthened our expectation that small doses of phenothiazines intrathecally might be as effective as large oral doses.

METHODS AND MATERIALS

During the period January—May 1963 a total of 11 patients were treated at the Weskoppies Hospital, Pretoria. They were grouped as follows:

8 patients with acute schizophrenia { 7 catatonic type, 1 hebephrenic type
3 patients with chronic schizophrenia, catatonic type

The method of treatment was as follows:

They were given one electroconvulsive treatment each, followed by 5 mg. of trifluoperazine in aqueous solution intrathecally the same day. This was followed the same evening by 40 mg. of trifluoperazine orally plus antiparkinsonism drugs (orphenadrine hydrochloride, 'disipal', 5 mg. for each 10 mg. of trifluoperazine, until the dosage of trifluoperazine was reduced to 10 mg. *b.d.*). The next 2 days they received 20 mg. of trifluoperazine twice a day; the following 2 days 10 mg. twice a day; then 5 mg. *b.d.* for two days and then 1 mg. *b.d.* as a maintenance dose.

In the hebephrenic case, thioridazine, 50 mg., was given intrathecally followed by 200 mg. orally, *b.d.* for 14 days. It was then reduced to 25 mg. orally once daily.

RESULTS

The results in all the cases can only be described as dramatic.

The 7 patients with acute schizophrenia, catatonic type, started to speak (on the average) from within ¾ - 1½ hours after the intrathecal injection. All were coherent and clear in their minds the following day. The second day after the initial treatment, 5 of the 7 were orientated for time and/or place with no hallucinations detectable. All 7 were apsychotic on the fourth day and had insight into their surroundings, and they were able to give a fairly accurate description of events leading to the start of illness up to the time of admission. Average hospitalization after this was about 7 - 8 weeks—purely for observation. Of the seven so treated not a single one showed any side-effects or relapses. The only adverse sign shown was a slight temperature rise up to about 99·6° F. the first evening. Routine CSF analyses showed no change except in one where epithelial cells were found.

ILLUSTRATIVE CASE REPORTS

E.M., aged 30 years, was admitted to hospital on 31 December 1962. Physically no abnormality was detected. She was dull, withdrawn, and asocial. She had to be spoonfed, and she was mentally mute and inaccessible. She showed no reaction to any stimulation. She had retention of saliva, typical waxy flexibility, and her personal habits were faulty. When not helped she sat or stood in one place all day. We observed her for a week with no change in the clinical picture. On 7 January 1963 she was given electroconvulsive therapy at 8.30 a.m., without response. During lunch she still had to be fed. At 3 p.m. we administered 5 mg. of trifluoperazine intrathecally. At 4.30 p.m. she started to talk in a whispering tone, but coherently. She enjoyed her supper, feeding herself. The next day, 8 January 1963, she again fed herself during the day and reported that she had been in hospital for a week and had been in this condition for close on 3 months. She stated that during this period she wanted to speak and react, but was not capable. In the evening she was given 50 mg. of trifluoperazine orally and on the next day 20 mg. of trifluoperazine twice a day. On this day, 9 January 1963, she could give a further account of herself as well and was correctly orientated for time and place. She admitted to previous auditory hallucinations, but stated that they were no longer present. She was clinically apsychotic. On the third day after treatment the dosage was brought down to 10 mg. of trifluoperazine, 2 days afterwards to 5 mg., and 2 days later to 1 mg. twice a day. She was kept for further observation for 6 weeks and did not relapse or exhibit side-effects.

The one hebephrenic treated with thioridazine showed a similar picture, although she did not improve as rapidly as the catatonics treated with trifluoperazine.

The hebephrenic schizophrenic was a Bantu female, 28 years of age. She was admitted on 12 February, being restless, rowdy, cursing, and not able to give an account of herself. She was manneristic and laughed inanely most of the time. She was objectively as well as subjectively hallucinated, describing voices of dead people speaking to her. She was treated with chlorpromazine, 100 mg. twice a day orally, up to 26 February 1963, when the use of chlorpromazine was discontinued. The only change noted to date was a fair reduction of symptoms. On 27 February she was given 50 mg. of thioridazine ('melleril') intrathecally. The patient was stuporose for two days, but on 3 March she denied all hallucinations, although still disorientated for time and place. She was put on 200 mg. of melleril orally twice a day. She was apsychotic and with full insight on 10 March. She was kept on 200 mg. of melleril orally twice a day until 13 March, and then drastically reduced to 25 mg. once a day. Although apsychotic she was kept on this dosage until the end of March, when all medication was stopped. She was discharged at the end of April, still apsychotic and with no signs of relapse.

The results in the 3 chronic catatonics were not as dramatic. They all came out of the stupor, but relapsed, although not so deep as before. We have found that they could help themselves—their intimate habits were corrected and they started to help with ward activities.

DISCUSSION

The results obtained by the intrathecal administration of phenothiazines in acute catatonics were dramatic. All patients responded, and the duration of treatment was drastically shortened.

Three possible reasons for this marked improvement suggest themselves:

1. That the relative impermeability of the blood-brain barrier in schizophrenia acts as a definite barrier to oral treatment in preventing a sufficiently high concentration of phenothiazines from reaching the brain.

2. If we accept the volume of CSF to be about 1/40th that of the blood volume, the following would apply: To get 5 mg. of trifluoperazine into the CSF would need an oral dose of 400 mg. if the drug reached the CSF in a *pro rata* rate. But, in reality, this would have to be much more. Van Loon *et al.*[5] have demonstrated the existence of an enterohepatic circulation and have shown that 70% of trifluoperazine[3,5] appeared in the bile within 10 hours. They also showed that in dogs, given pharmacological doses, the systemic and hepatic blood levels were low and

did not exceed 10 micrograms per ml. at any one time. Moreover '. . . during the first 4 - 6 hours of collection, the portal blood contained 2 to 3 times as much drug as did the hepatic blood, demonstrating the rapid removal of phenothiazine from the blood by the liver . . .'

Further, the rate of CSF circulation is very low, and consequently there is a more prolonged exposure to the phenothiazines introduced intrathecally. This supposition would accord well with Berti and Cima's conclusion[6] '. . . one fact should be stressed: from the evidence obtained from different experimental conditions a good relation seems to exist between the psychopharmacological effects of the phenothiazines and the structurally related psychoactive drugs, and the amount of unchanged drug in the brain . . .'

3. The phenothiazines are probably not metabolized to any extent in the CSF.

This may well be the reason why no side-effects occurred in this trial—a remarkable feature. Although an antiparkinsonism drug was given for 5 days only, not even minor side-effects developed. It has never been definitely decided whether the occurrence of extrapyramidal symptoms are due to the phenothiazine or to one of its metabolites.

It would thus appear that our hypothesis that the intrathecal injection of psychotropic drugs could produce a quicker response, is proved. However, this preliminary report calls for further investigation and confirmation.

SUMMARY

A hypothesis was proposed that the intrathecal injection of psychotropic drugs could possibly shorten the treatment of certain mental diseases by circumventing the blood-brain barrier.

It was shown to be the case in 11 patients with schizophrenia (7 acute catatonics, 1 hebephrenic and 3 chronic catatonics) who received one electroconvulsive treatment and 5 mg. of trifluoperazine intrathecally, followed by oral dosage. The response was dramatic and rapid and patients started to speak from within ¾ – 1½ hours after injection. The 7 acute catatonics were apsychotic after 4 days. One hebephrenic was treated with thioridazine, 200 mg., intrathecally and responded well too. The response was not so marked, however, in the chronic catatonics.

A remarkable feature was the absence of any side-effects. A possible reason for this is suggested.

PART II. THE USE OF AN ANTISEROTONIN SUBSTANCE INTRATHECALLY

Encouraged by the results obtained with intrathecally administered phenothiazines in schizophrenia, it was decided to try an intrathecally administered antiserotonin agent in acute mania and intractable anxiety states.

The arguments for this route of administration were the same as that for phenothiazines—it was hoped to circumvent the blood-brain barrier and obtain a high concentration in the CSF.

The drug chosen for this trial was methysergide (1-methyl* lysergic acid butanolamide), which has been shown to be about 4 times as active as LSD 25 in antagonizing the action of 5-HT on plain muscle[7,8] and other pharmacological tests, including the serotonin oedema of the rat's paw *in vivo*.[8]

Since the action of the MAO inhibitors in the treatment of depression is that of raising the concentration of 5-HT in the brain, it seems reasonable to suppose that in patients with acute mania there may be an increased 5-HT activity in the brain, and treatment with an antiserotonin substance may be indicated. Moreover, Cerletti found that 'deseril' (methysergide) clearly reduced emotional tension as expressed by the defaecation reaction in experimental animals.[8]

*Deseril.

METHODS AND MATERIALS

4 Patients with acute mania, and 2 patients with neurotic anxiety, who had failed to respond to the usual treatments, including ECT, were given 2·5 mg. of methysergide (deseril) intrathecally.

RESULTS

The results in the 4 patients with acute mania were remarkable. Here again the onset of relief of symptoms was initiated within 1 - 1½ hours. The patients calmed down and were easily managed in a very short time. The only side-effects noted were that some of them remained sleepy, yawning frequently, for 1 - 2 days. No relapse was found, nor a shift to depression. They were all kept for observation for from 8 to 10 weeks, and eventually discharged.

Intrathecal deseril was also used in 2 White female patients with neurotic anxiety.

The first patient had had 3 previous admissions to mental institutions during the preceding 5 years. During the last admission to this hospital she had exhibited extreme fear and anxiety. During the 4 months preceding the intrathecal administration, she ran the gamut of treatment by her therapists with no lessening of the intense fear response she was showing. She had a course of electroconvulsive therapy and various anti-anxiety drugs, as well as intensive psychotherapy—all to no avail. On 12 February 1963 she was given 2·5 mg. of methysergide intrathecally and, having had lumbar punctures done before, this was no novelty to her, and she was not informed of our intention of giving her deseril intrathecally. An hour later she calmed down. On the third day it was possible to discuss the fear-prevailing situations, and she was generally more amenable to psychotherapeutic measures and appeared calm. Within 3 months she was discharged as being much improved. The only side-effect noted was the feeling of drowsiness for the 2 days subsequent to the intrathecal administration of methysergide.

The same subsiding of anxiety was noted in the second patient—following intrathecal administration of methysergide.

DISCUSSION

The remarkable results obtained in the 4 patients with acute mania seem to justify our rationale in using methysergide for treatment of acute mania. Whether the mode of action can be explained by methysergide antagonizing 5-HT needs further investigation, however. The mode of action in the 2 patients with neurotic anxiety is in conformity with the animal experiments reported by Cerletti *et al.*[8] The rationale may lie in the structural relationship between 5-HT and methysergide, e.g. by way of competitive effect.

These theories, however, are only proposed as a possible mode of action and much work remains to be done to prove or disprove them.

SUMMARY

The treatment of the 4 patients with acute mania and 2 with neurotic anxiety by the intrathecal administration of methysergide (2·5 mg.) is described.

The results were remarkable in that in the 4 patients with acute mania relief of symptoms was initiated within $1-1\frac{1}{2}$ hours, and patients were apsychotic within days. The 2 patients with neurotic anxiety, who had had the gamut of treatment, also responded to this treatment.

A possible mechanism of action is suggested but this needs further investigation.

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