sterile water is started. The injection is given slowly at the rate of about 1 ml. per minute until the patient falls asleep and can tolerate a lubricated artificial airway. The dose required varies from 20 to 45 mg. of chlorpromazine and 40 to 90 mg. of pethidine. During induction a few patients complain of thirst or palpitations, but these are of short duration. Patients even at this stage are often just capable of responding to shouted instructions, but in a most apathetic way, and their efforts are poorly maintained. On questioning afterwards they have no recollection of this; on the other hand, there appears to be no retrograde amnesia, and all remember coming to the anaesthetic room.

A regional infiltration with procaine is given, coupled with a retrobulbar injection. A long, narrow-bore tube connected to an oxygen cylinder is placed beneath the face towel so that the open end is in close proximity to the artificial airway in an attempt to keep the air circulating beneath the towels and increase the oxygen concentration.

The patient sleeps peacefully throughout the operation, and the operator can take as long as he wishes without the fear of a restless patient. After the operation patients cause the minimal amount of trouble in the ward, and the method has been well received by the ward sister. After one to two hours patients will often remove their own airways. Unless disturbed, they sleep for the remainder of the 24 hours. If roused they answer questions with progressively more enthusiasm, and quickly drop off to sleep again. Next morning they have all appeared normal, the majority having no recollection of the previous 24 hours.

Results

Since March, 1954, 80 patients have been anaesthetized in this way. Their ages ranged from 18 to over 80 years, the majority being between 60 and 80 years. Three-quarters of this number were undergoing cataract operations, and the remainder operations for glaucoma and corneal grafting. There has been no mortality or morbidity in this series, and the patients' post-operative condition has been excellent. Although the method has not been used on the extremely frail and those with severe cardiac disease, it has been used for nervous patients, and also in many cases with marked signs of arteriosclerotic cerebral degeneration where a purely local technique would have been dangerous.

In one case vomiting occurred four hours after the operation, but it was of very short duration, and in this case there was a history of many years' "gastric trouble." With this exception there has been no coughing or straining in the post-operative period and recovery has been extremely quiet and uneventful. Two cases of severe hypertension, both with a pre-operative systolic blood pressure of over 250 mm. Hg, caused some anxiety in the post-operative period. Soon after injection of the chlorpromazine-pethidine mixture the systolic blood pressure in both cases fell to between 70 and 90 mm. Hg, and it remained at this level for just over three hours post-operatively. Apart from the hypotension, the physical state of these two patients appeared satisfactory and the pulse remained slow and easily palpable. At the end of three hours the blood pressure began to rise slowly in each case, and returned to the pre-operative level in 12 hours. Both patients made an uneventful recovery.

Summary

A method of anaesthesia for use in intraocular surgery has been described, the agent being a mixture of chlorpromazine hydrochloride and pethidine.

The results obtained in 80 cases have been briefly recounted.

The main advantages of the method are: (1) no co-operation is required from the patient during the operation or for several hours afterwards; (2) it produces a low-tension eye ideal for intraocular surgery; and (3) the recovery period is extremely tranquil.

LIVER DAMAGE AND EOSINOPHILIA FOLLOWING CHLORPROMAZINE THERAPY

REPORT OF A CASE

BY

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A relationship between chlorpromazine therapy and liver damage has been recognized. The extent of liver damage varies; at least one fatal case has been reported (Boardman, 1954). Lemire and Mitchell (1954) mention the occurrence of transient eosinophilia during chlorpromazine jaundice. The present case report also illustrates this unusual phenomenon.

Case History

The patient, a man aged 52, was of Jewish extraction. During the last four years, electric convulsion therapy had been given elsewhere on some 30 occasions for a recurring depressive state. Between March 31 and April 12, 1954, chlorpromazine was administered orally, the total dosage being 1.5 g. His previous medical history and family history were not relevant. About ten days after beginning this treatment he became nauseated. During the next three days he became febrile and began to vomit. He complained of pain in all his joints, frontal headaches, rigors, loss of appetite, and colicky abdominal pain; he developed a continuous burning pain in the epigastrium. Chlorpromazine was suspended. Admission was arranged to the Royal North Shore Hospital of Sydney on April 19.

Physical examination revealed a well-developed middle-aged man who was obviously jaundiced. His temperature was 102.2° F. (39° C.). The liver was not palpable, but there was generalized abdominal tenderness, maximal in the right hypochondrium. There were no splenomegaly, no glandular enlargement, and no abnormality on rectal examination. The blood pressure at the time of admission was 75/50. Subsequent readings were in the order of 100/70. The urine was very dark, and analysis revealed the presence of bile pigments, bile salts, and an excess of urobilinogen. The first faecal specimen examined after admission was pale.

On April 19 the leucocytes numbered 15,300 per c.mm., of which 49% were eosinophils. On the 20th the white cells totalled 14,900 per c.mm. (eosinophils 58%); the serum proteins were 7.9 g.%, the albumin-globulin ratio was 2.4:1; the thymol turbidity was 1 unit (normal range 0-4); the serum alkaline phosphatase was 12.8 modified Bodansky units (normal range 2.2-8.6) (Shinowara *et al.*, 1942); and the serum bilirubin was 3.8 mg. per 100 ml. The Casoni test was negative, and no ova, cysts, or parasites were found in the stools. The chest x-ray findings were normal; the plain x-ray film of the abdomen showed no gross abnormality; repeated examinations of the stools for occult blood were negative; and the Eagle flocculation test was negative. Three days after admission the temperature had fallen to normal. A slight subjective improvement had occurred but he remained deeply jaundiced.

By April 30 the diagnosis had not been established, so it was decided to perform liver biopsy by needle aspiration. This was done on May 3. The section showed bile pigment in the bile canaliculi, mainly near the centres of the lobules. There was no accumulation of bile in the bile ducts of the portal tracts. The liver cells appeared healthy throughout. Some of those near the centres of the lobules had bile in their cytoplasm. In the supporting tissue of the

portal tracts there were more lymphocytes and histiocytes than normal. The fibrous tissue was not increased. The Kupffer cells contained no bile pigment. A diagnosis of biliary obstruction was made.

Laparotomy was performed on May 10. The gall-bladder was normal and the common duct was not dilated. On opening the duct there was only a moderate flow of bile. A probe was passed towards the porta hepatis. However, neither the right nor the left intrahepatic duct could be entered, and it was thought that there was an obstruction at the origin of the intrahepatic portion of the common duct. The common bile duct was drained, using a T-tube. No abnormality was found on palpation of the other intra-abdominal organs.

Apart from a low-grade post-operative fever, due to a pulmonary infection, and mild colicky abdominal pain, convalescence was uneventful. The quantity of bile which drained ranged from 75 to 480 ml. daily from the first to the tenth post-operative days. These figures are within normal limits (Rundle *et al.*, 1955).

Nine days after operation (May 19) a cholangiogram was done. The gall-bladder and bile ducts filled well and appeared normal. The biliary drainage tubes were removed on May 26. At this time the degree of jaundice was lessening (serum bilirubin 3.8 mg. per 100 ml.) and the patient was beginning to regain his appetite and to feel well. The eosinophils had fallen to 5% of 16,300 cells.

Improvement was steadily maintained, and when discharged on June 12 the jaundice had almost completely subsided and the patient was feeling well.

When last seen, on December 23, he appeared to be perfectly well; in the interim further shock treatment had been given. The serum bilirubin, the serum proteins, and the thymol turbidity values were normal, but the urinary urobilinogen was still increased. The total white cell count was 10,950 per c.mm., and 6% of these were eosinophils.

Discussion

Both the patient and his wife were convinced at the time of admission that the illness had resulted from chlorpromazine, and his medical attendants at first thought that he was suffering from hepatitis. It was necessary to distinguish between an obstructive jaundice and a hepatocellular jaundice. In favour of the former were the presence of dark urine containing bile pigments and salts, the pallor of the stools, and the rising level of the serum alkaline phosphatase. However, it was difficult to explain the presence of excess urobilinogen in the urine if this really was an obstructive lesion.

The presence of eosinophilia suggested the possibility of an allergic process. Hodgkin's disease was considered, but there were no enlarged glands and the spleen was not enlarged. Parasitic causes of eosinophilia were sought but were not found.

The results of the liver biopsy suggested an obstructive lesion, but this could not be definitely demonstrated at operation. In fact, the post-operative cholangiogram showed the biliary tree to be normal. A careful review of sections of the liver biopsy has since been made and the appearances are now considered to be those described in the so-called cholangiolitic hepatitis (Watson and Hoffbauer, 1946; Goulston and Smith, 1951).

It would appear, therefore, that this patient was suffering from a form of hepatitis. The biochemical investigations may be explained on the basis of hepatitis with obstruction.

Infective hepatitis must be considered in the differential diagnosis, especially as it is common in the Sydney community at present. Eosinophilia does not appear to have been reported in this disease. On the contrary, it is stated (MacCallum *et al.*, 1951) that eosinophils are commonly absent in infective hepatitis. In this case the total number of eosinophils increased, attaining the high percentage of 58 at the height of the illness.

It is interesting that Lehmann and Hanrahan (1954) have noticed the occurrence of allergic reactions, such as urticaria and asthma. In their series of 71 patients treated over a period of four months with chlorpromazine, 13% showed such reactions. However, they do not mention eosinophilia. In our patient the eosinophilia may have been indicative of an underlying allergic reaction.

Lemire and Mitchell (1954) observed three cases of chlorpromazine jaundice in elderly people. In two of these patients a transient eosinophilia of 7 to 17% was noted. The liver-function tests revealed a hyperbilirubinaemia, an increased serum alkaline phosphatase, and a normal thymol turbidity. Two had liver biopsies performed, and all three were subjected to surgery. The authors consider that their patients were suffering from toxic hepatitis due to chlorpromazine, the mechanism of the complication being unknown. Their findings and conclusions correspond with our own.

Further observations will be necessary to establish whether our patient has sustained permanent liver damage as a result of chlorpromazine therapy. The presence of excess urobilinogen in the urine six months after apparent recovery does suggest this.

Summary

A case of hepatitis following chlorpromazine therapy is reported.

The occurrence of eosinophilia in this illness is discussed.

I wish to thank the General Medical Superintendent of the Royal North Shore Hospital of Sydney for permission to report this case; and Dr. F. A. E. Lawes, Mr. F. F. Rundle, Dr. I. D. Thomas, and Dr. K. Viner Smith for assistance in preparation of the paper.

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Medical Memoranda

Anaesthesia Following Long-term Oral Chlorpromazine Hydrochloride Therapy

A review by Dundee (1954) of the pharmacology and applications of chlorpromazine hydrochloride records the widespread clinical uses of this drug outside hospital practice, and the increasing possibilities of anaesthetists meeting emergency admissions so treated. The following case is put on record so that others may avoid "anaesthetist's distress" in similar cases.

CASE REPORT

A feeble-minded man of 20, weight 11½ stone (73 kg.), was admitted in February, 1955, with a diagnosis of acute appendicitis. He was given ½ gr. (22 mg.) of "omnupon" and 1/150 gr. (0.43 mg.) of scopolamine one hour before operation, and was induced with thiopentone sodium 600 mg., and maintained with gallamine triethiodide, 100 mg., nitrous oxide and oxygen, and ether. There was a delayed return of normal respiration for three-quarters of an hour.

At operation a gangrenous retrocaecal appendix was removed. The operation lasted for one hour and he did not regain consciousness for the next four and a half hours,