The relation of the Q-T interval to various physical, chemical, and pathological states is discussed.

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CHLOROQUINE IN THE TREATMENT OF AMOEBIC LIVER ABSCESS

BY

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The antimalarial action of the derivatives of the 4-aminoquinoline series was thoroughly established during the last war, and from among the series chloroquine (7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline diphosphate) was found to be one of the most effective compounds, and to be of low toxicity. Observations revealed that the drug had a peculiar depot action, being stored in the liver in concentrations as high as 500 to 600 times the plasma level (Conan, 1948). This property of the drug, as well as its pronounced antiplasmodial activity, led to the testing of its possible efficacy in protozoan infections other than those caused by malaria plasmodia. Tests carried out in England and America immediately after the war showed that it had a pronounced action in *Entamoeba histolytica* infections of the liver that were responsible for hepatic amoebiasis and liver abscesses. These experimental findings now seem to be generally confirmed by clinical trials.

Conan (1949) used chloroquine successfully in seven cases of amoebic hepatitis and found that it was an effective chemotherapeutic agent for the treatment of amoebic infections of the liver, being at least as effective as emetine but apparently without the latter's toxicity. In the same year Manson-Bahr (1949) reported his experience with chloroquine in a case of *E. histolytica* liver abscess in a very advanced stage, which could not

be influenced either by emetine or by streptomycin and penicillin. Fever and other symptoms persisted in spite of the latter. He then resorted to treatment with chloroquine and observed a prompt recession of the symptoms. The temperature was soon brought down to normal, and healing of the abscess was claimed after a fortnight's treatment. Similar results were reported by Murgatroyd and Kent (1948) in their case of liver abscess, which had proved very resistant to emetine, di-iodohydroxy quinoline, streptomycin, penicillin, and local emetine lavages. More comprehensive work on the subject has been reported by Harinasuta (1950, 1951), working in Siam, where hepatic amoebiasis is of frequent occurrence. In his first paper he reported nine cases of amoebic liver abscess (two with pulmonary complications) successfully treated with chloroquine. Later he made a comparative study of the action of chloroquine and emetine in amoebic liver abscesses, putting 45 cases on chloroquine treatment exclusively and an equal number of cases on emetine. In conclusion, Harinasuta remarked: "In comparison with emetine, chloroquine appeared to possess as much curative value in the treatment of amoebic liver abscess. It might be somewhat inferior on the point of relapse rate; but in other respects it had its own advantages—e.g., peroral administration, tolerability, and low toxicity in general—so that it might be employed even in cases in which emetine was contra-indicated." Among the side-effects of chloroquine Harinasuta listed nausea, vomiting, mild diarrhoea, transient pruritus, disturbance of ocular accommodation, and also a slight fall in the blood pressure. He noted, however, that these side-effects were usually mild and insignificant and only transitory in nature.

Among the publications by Indian research workers reference may be made to those of Sharma *et al.* (1951) and of Subramaniam (1951). The former reported on two cases of amoebic liver abscess from Bangalore which proved resistant to treatment with emetine, vitamin B-complex preparations, sulphonamides, and penicillin. At the time of chloroquine therapy the patients appeared to be so gravely ill that their chances of recovery seemed to be extremely small. The authors concluded: "Our impression was that the administration of chloroquine marked a turning-point in an otherwise downward course. Our cases are in line with the striking results by chloroquine reported by others, and the drug marks a definite advance in the treatment of amoebic hepatitis, especially cases with abscess formation." Subramaniam used chloroquine diphosphate only in four cases of amoebic hepatitis, but claimed good results with this exclusive treatment. He stated that in all cases the temperature subsided within 24 to 48 hours, there was a marked lessening of the pain, and the patient felt better.

Present Series

I have used chloroquine diphosphate ("resochin") in a series of 11 cases of amoebic liver abscess, and the results obtained seem to confirm the observations of others that this drug has advantages in the treatment of extra-intestinal infections with *E. histolytica*.

The patients were admitted to the King Edward Memorial Hospital or to the P.G. Singhanee Hindu Hospital, and were kept there throughout the course of treatment. They were asked to return if there were any symptoms suggesting relapse, and each was given a postcard to be filled in by a doctor treating him for the complaint. Each patient also received another card with particulars of the previous history and treatment given.

The diagnosis of amoebic liver abscess was based upon the history of the clinical signs and characters of the pus aspirated by liver puncture. One patient with enlarged tender liver, raised temperature, and leucocytosis was negative on aspiration; he was treated with chloroquine without success. Fluoroscopy was carried out to show the movement and elevation of the dome of the diaphragm and the condition of the lungs and pleura. In every case the blood was examined for evidence of leucocytosis and was repeated in some cases during the course of treatment. It was only after the diagnosis was established by aspiration of pus that treatment with chloroquine was instituted. Emetine was not given in any case. The dosage of chloroquine was one tablet (0.25–0.15 g. of base) twice a day, preferably after food, for a period of 10 to 12 days in the first six cases. After two of these cases had relapsed the length of treatment was increased to 30 days. The initial higher dosage advocated by Conan (1949) and used by most workers was not adopted because of the untoward reaction noticed in a case of amoebic hepatitis not included in the series. As Indians are of small size, the lower dosage was more likely to be tolerated, with fewer untoward reactions. The drug was given for a period of 30 days in a case of relapse. It was not administered by the parenteral route.

Eleven cases (nine male, two female) of amoebic liver abscess were treated during a period of two years. As there were rigid criteria for diagnosis, not all the cases of liver abscess were taken for study, particularly if there was any doubt about whether emetine had been given before or during hospital treatment. In some cases sulphadiazine and antibiotics were given for the lung and abdominal conditions. Details of the cases are shown in the Table.

Details of 11 Cases of Amoebic Liver Abscess

Case No.	Age	Sex	Result of Liver Aspiration	Stool Exam. for <i>E. histolytica</i>	Treatment Schedule		Day of Normal Temp.
					Daily Dose	Length of Treatment	
1	32	M	400 ml.	Neg.	0.5 g.	10 days	5th
2	45	M	200 "	"	0.5 "	12 "	2nd
3	29	M	50 "	"	0.5 "	12 "	3rd
4	46	F	50 "	Pos.	0.5 "	10 "	"
			50 "	Neg.	0.5 "	2 "	Died 3rd day
5	40	M	600 "	"	0.5 "	11 "	2nd
6	30	M	100 "	"	0.5 "	30 "	3rd
7	32	M	250 "	"	0.5 "	10 "	4th
8	37	M	200 "	Pos.	0.5 "	30 "	3rd
9	29	M	400 "	Neg.	0.5 "	30 "	2nd
10	36	F	50 "	"	0.5 "	30 "	"
11	44	M	300 "	"	0.5 "	30 "	3rd
			200 "	"	0.5 "	21 "	2nd

E. histolytica was found in the stools in two cases. The temperature subsided within 72 hours in most cases, and within 48 hours in five. In some cases in which the temperature was normal after aspiration of the abscess it did not rise after the drug was given. The patient felt better by the fourth day, and had an improved appetite. All patients gained weight—as much as 20 lb. (9 kg.) in a month in one case. A lessening of liver tenderness was the first sign of improvement, and the lower margin of the liver soon disappeared from below the costal margin. The leucocytosis subsided in about a week in those cases in which examinations were made. No attempt was made to measure any changes in blood pressure, as observed by Harinasuta (1950, 1951), but no overt effects of a lowered blood pressure were noticed. Apart from mild nausea in two cases and dimness of vision in one, toxic symptoms of the drug were not recorded. Nausea, gastro-intestinal irritation, itching, and changes in accommodation in the eyes were noted in one case (not included here) when the initial dose was double that used in this series.

Relapses

Two patients were readmitted with recrudescence of the disease, one of them three months and the other four

months after treatment with chloroquine for 10 days. In both cases pus was again aspirated. One of them (Case 4) died two days after the second admission, before chloroquine had any chance of action. This patient had a pulmonary complication. Case 5 was again treated with chloroquine, 0.5 g. a day for four weeks, with complete success.

Harinasuta (1951) had 10 relapses in a series of 45 cases which responded to further chloroquine treatment—a relapse rate of 22.2%. They occurred after a two-weeks or a three-weeks course of treatment. In the present small series the relapse rate was two in six (33.3%) after 10 to 12 days' treatment at a lower initial dosage. Harinasuta observed a definite refractoriness to a single course of chloroquine in two patients, both of whom died. Similar drug-resistance has been recorded with emetine.

Discussion

Conan (1949) advocated a three-weeks course of treatment, and subsequent workers have more or less followed the same course with satisfactory results. More than one-fifth of Harinasuta's (1951) cases required a second course of treatment, as did two of the first six cases in the present series. Relapses occur also with emetine and require further treatment. In order to avoid relapse the period of treatment in the remaining cases was increased to 30 days—longer than that advocated by Conan. From published work it seems obvious that the drug has a definite curative action on amoebic liver abscess, and it is the impression of most workers, including myself, that it acts more quickly than emetine and without the latter's harmful effects. It can be given when the general condition of the patient is poor and when emetine would be contraindicated and even harmful. Unlike emetine, it has no general toxic action and can be given orally. The dosage and the length of treatment so far used by most workers, even though satisfactory in most cases, needs evaluation by further clinical trials.

Relapses occur more often with smaller doses of shorter duration. They occurred even with the dosage advocated by Conan. Harinasuta (1951) had to use as many as five three-weeks courses in one case. From this it is obvious that the dosage advocated by Conan should be increased in length to four or even six weeks, as the drug can be taken by mouth and has no major untoward effects on the body. Conan's three-weeks course may be adequate for amoebic hepatitis, but not in all cases of abscess. In the present series cases of abscess and not of hepatitis were treated, as the value of the drug in the treatment of undoubted cases of liver complication of amoebiasis had to be established.

Extended clinical trials with a good follow-up should be undertaken in order to evaluate the length of treatment with chloroquine in cases of abscess. At present the drug is not readily obtainable, but when it is freely available and cheaper such a trial would be possible. Harinasuta (1951) advocated a combined treatment with emetine. I consider, in the light of present available knowledge, that a prolonged course of treatment is all that is necessary. A therapeutic trial with chloroquine can safely be carried out in cases of liver enlargement in which diagnosis is doubtful, and liver abscess can be easily excluded by such a trial, without any of the harmful toxic actions which accompany emetine therapy.

Summary

Eleven cases of amoebic liver abscess, three with pulmonary complications, were treated with chloroquine diphosphate with very good results. The dosage was 0.5 g. a day. It was found that treatment for 10 to 12 days was adequate in four out of six cases: two relapsed, but responded to further treatment. In the remaining cases the drug was given for 30 days. One patient died during a relapse. It is suggested that further work

should be carried out in order to determine the dosage of the drug required and the length of its administration in the treatment of the abscess. Minor toxic symptoms were observed. The drug can be safely used as a therapeutic test if diagnosis is doubtful.

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“DANGEROUS RECIPIENTS” OF TRANSFUSION

INCOMPATIBLE REACTIONS AFTER TRANSFUSION OF GROUP O Rh-NEGATIVE BLOOD

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The following case reports are placed on record to re-emphasize that Group O Rh-negative blood is not free of potentially dangerous blood-group factors, and that inexperienced medical staff are not suitable persons to undertake the matching of blood for transfusion.

Case 1

A multiparous woman aged 26, known to be Group O Rh-positive, was delivered of her third baby by elective caesarean section. Because of haemorrhage during the operation a transfusion of 2 pints (1,140 ml.) of blood became necessary, and the house-surgeon “matched” two bottles of Group O Rh-positive blood against the patient's serum by a saline slide technique. No incompatibility was detected, but on the day after the transfusion the patient was noticed to be “slightly jaundiced.” The baby also had developed a definite jaundice within a few hours of birth, but since the mother was Rh-positive and the baby's haemoglobin was 140% (20.7 g. per 100 ml.) the possibility that the mother's serum contained irregular blood-group antibodies was not considered.

Seven days later the mother's general condition was unsatisfactory and her haemoglobin 35% (5.2 g. per 100 ml.). Transfusion of a further 2 pints (1,140 ml.) of blood was therefore prescribed, and on this occasion the house-surgeon selected and matched 2 pints (1,140 ml.) of Group O Rh-negative blood, presumably as a safeguard against a haemolytic transfusion reaction. No incompatibility was detected, but the transfusion was discontinued after 1½ pints (850 ml.)

had been transfused because the patient had developed a severe rigor. During the next 48 hours she had jaundice and oliguria. Although her haemoglobin remained at 35% (5.2 g. per 100 ml.) she refused any further transfusion and made a gradual recovery to normal health during the next six to eight weeks.

Laboratory investigations showed the patient's blood to be Group O Rh-positive, Rh genotype cDE/cDE, and that the transfused Rh-negative cells had undergone haemolysis. Immune antibodies, type anti-e + anti-C, were demonstrable in the patient's serum to a titre of 256 with homozygous e-positive red cells (Rh-negative cells, cde/cde) suspended in saline and in albumin. The titre against heterozygous cells (R₁R₂CDe/cDE) was 64.

Inquiry into the patient's previous history revealed that she had been transfused with 4 pints (2,270 ml.) of blood (Rh group unknown) at her first pregnancy seven years before, because of a severe accidental haemorrhage, and was subsequently delivered of a stillborn macerated foetus. Her second pregnancy, three years later, had resulted in the delivery of a healthy female child who had shown “a slight jaundice” shortly after birth, but whose subsequent progress was uneventful. The third baby, the outcome of the pregnancy under discussion, was subsequently found to be Group A, R₁R₂ (CDe/cDE); a direct antiglobulin (Coombs) test on its red cells was positive, and by the twenty-ninth day of life its haemoglobin had dropped to 42% (6.2 g. per 100 ml.). After a transfusion of Group O blood of genotype cDE/cDE it made a satisfactory recovery.

Case 2

A woman who had had two normal children received an emergency blood transfusion (group unknown) during an air raid in 1941. Later she had one normal full-term child and then two miscarriages, each being a six-months foetus. At the age of 42 she was admitted to hospital because of menorrhagia. After a few days in hospital she had a sudden haemorrhage at night, and a resident house-surgeon transfused a pint (570 ml.) of Group O Rh-negative blood in emergency and without previous direct matching. At the same time another member of the resident medical staff “matched” a further bottle of Group O Rh-negative blood for her by a slide technique, but transfusion of this blood was found not to be necessary. Nine days later it was decided to transfuse this “matched” blood so that the patient might be made fit for curettage. She developed a rigor at the conclusion of this transfusion, followed by jaundice, haemoglobinuria, and oliguria for the next seven days.

Serological investigations demonstrated the patient to be Group O Rh-positive, Rh genotype CDe/CDe. Immune antibodies of the type anti-c + anti-E were demonstrable in the post-transfusion sample of her blood to a titre of 32 in saline and 256 in albumin against homozygous c-positive cells (Rh-negative cells, cde/cde), and 2-4 in saline and 16-32 in albumin against heterozygous c-positive cells (R₁R₂, CDe/cde). The patient's post-transfusion sample contained no Rh-negative cells, thus confirming that the blood transfused was incompatible.

Comments

Both these patients nearly lost their lives, and both suffered severe renal damage, because of the transfusion of Group O Rh-negative blood. Fortunately, although Rh-negative corpuscles contain the Rh antigens c, d, and e, and may contain other antigens such as Kell, Fya, and S, which are known to have been the cause of similar haemolytic transfusion reactions, few patients requiring transfusion possess the corresponding antibodies, anti-c, anti-e, anti-Kell, etc., in their plasma. In consequence incompatible transfusions from this cause remain a rarity. The fact, however, that immune antibodies of this type may be present in the circulation of certain patients, even on rare occasions, constitutes a challenge, and, by a more thorough applica-