the first symptom of gastro-duodenal disease occurred less than a year before admission for pyloric stenosis there was an almost even chance of malignancy. Bockus (1943) records similar findings. Neither the length of obstructive history nor the failure of regular aspiration to reduce the volume of the gastric residue was of value. A history of previous ulcer dyspepsia of some years' standing did not preclude carcinoma. As surgery is the only certain remedy for pyloric stenosis, whatever the cause, this clinical differentiation is not of great importance.

In the present series medical treatment, with repeated gastric aspiration or lavage, replacement of fluid and electrolyte loss, bed rest and frequent milk feeds, although an essential preliminary to surgery, was rarely tried as definitive therapy and never proved of lasting value. Emery and Monroe (1935) found benefit from such measures in 38.6% of their cases but gave no precise definition or data on length of observation after treatment. Bockus (1943) stated that 50% of patients improved by medical measures would relapse and need operative relief of their obstruction. In view of the low mortality associated with modern surgery, other definitive measures have been largely superseded. There were only two deaths in the present series among 92 patients treated surgically for pyloric stenosis due to benign ulceration. By contrast, only 4 of the 13 with carcinoma left hospital after a potentially curative operation.

Summary

A precise definition of pyloric stenosis, and the diagnostic criteria, are given. The clinical, radiological, laboratory, and morbid anatomical findings in 118 consecutive cases of pyloric stenosis are reviewed. Active duodenal ulceration was the commonest cause.

Diarrhoea attributable to pyloric stenosis was found in 20% of the patients in the series. Its causation is discussed. In other respects previous descriptions of pyloric stenosis have, in general, been confirmed.

The definitive treatment was surgical in nearly all cases.

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References

Berkman, D. M. (1921). *Med. Clin. N. Amer.*, **5**, 411.
—— (1923). *Coll. Pap. Mayo Clin.*, **15**, 92.
Bockus, H. L. (1943) *Gastro-enterology*, vol. 1. Saunders, London.
Crohn, B. B. (1927). *Affections of the Stomach.* Saunders, Philadelphia.
Dragstedt, L. R. (1956). *Amer. J. Roentgenol.*, **75**, 219.
—— (1958). *Brit. med. J.*, **1**, 1234.
Emery, E. S., jun., and Monroe, R. T. (1935). *Arch. intern. Med.*, **55**, 271.
Hinds, S. J., and Harper R. A. K. (1952). *Brit. J. Radiol.*, **25**, 451.
Hurst, A. F. (1946). In F. W. Price's *A Textbook of the Practice of Medicine*, 7th ed. Oxford Univ. Press, London.
—— and Stewart, M. J. (1929). *Gastric and Duodenal Ulcer.* Oxford Univ. Press, London.
Illingworth, C. F. W. (1953). *Peptic Ulcer.* E. and S. Livingstone Ltd., Edinburgh and London.
—— Scott, L. D. W., and Jamieson, R. A. (1944). *Brit. med. J.*, **2**, 655.
Johnson, H. D. (1955). *Lancet*, **1**, 266.
Jones, F. A., and Pollak, H. (1945). *Brit. med. J.*, **1**, 797.
Parsons, F. M., and Watkinson, G. (1954). *Postgrad. med. J.*, **30**, 145.

CHLOROQUINE PER RECTUM FOR MALARIA IN CHILDREN

BY

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The use of chloroquine in suppositories for the treatment of malaria in children was introduced seven years ago in to-day's Vietnam by Canet (1951). This method, advocated by Lavier and Schneider (1951), has subsequently been quite widely adopted in paediatric practice in French overseas territories. Nevertheless it is little known or used in other countries, and was not mentioned in the comprehensive monograph on chemotherapy of malaria by Covell, Coatney, Field, and Singh (1953).

As problems connected with treatment of malaria in children were recently reviewed by one of us in preparing a chapter on malaria for Trowell and Jelliffe's (1958) book on tropical paediatrics, it was proposed to assess the value of rectal administration of chloroquine on a selected group of hospitalized African children. We thought it would be of interest to evaluate not only the comparative parasiticidal action of the drug given per rectum or by mouth, but also to determine the respective rates of urinary excretion of the chloroquine base.

Material and Technique

The trial was carried out in the children's ward of the Royal Orthopaedic Hospital at Igbobi, near Lagos. Twenty-eight children who were admitted for various bone and joint diseases but who, on admission, were found to be also infected with malaria were selected for the trial. After a preliminary screening, the children, whose mean age was 6.8 years, were divided into two groups. One group of 10 received chloroquine sulphate by mouth in one single dose containing 300 mg. of chloroquine base. The other group, composed of 18 children, was subdivided, so that one subgroup comprising 12 children was given a single chloroquine sulphate suppository containing 300 mg. of base, while the other subgroup, consisting of six children, had one such suppository every day for five days, thus receiving a total dose of 1,500 mg. of chloroquine base.

All the children were on the same hospital diet, but the fluid intake was not controlled. The drugs were given personally by one of us, and thick blood films were taken daily for one week after the administration of chloroquine. The slides, stained with Giemsa, were examined for the presence of malaria parasites, their species, and the parasite density. The percentage of daily slides cleared of malaria parasites and the "clearance time" were used as an indication of the activity of the drug administered to each group. This method has been used for several similar investigations (Bruce-Chwatt, 1951; Bruce-Chwatt and Archibald, 1953; Bruce-Chwatt and Charles, 1957), and need not be described in detail.

The rate of absorption and excretion of the antimalarial was estimated from the amount of chloroquine base eliminated in daily samples of 24-hour urine during

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one or two weeks following the administration of the drug. The method used for chloroquine estimation in the urine was that of Fuhrmann (1950), which measures the turbidity produced in the acid solution of extracted chloroquine base after the addition of the Mayer–Tanret reagent. The original method was slightly modified so that only 100 ml. of urine was necessary.

The turbidity was measured in a Spekker H760 absorptiometer, using a 508 filter. The amount of chloroquine in the solution was estimated from a calibration curve prepared from known amounts of chloroquine sulphate. The value of this method was previously assessed by Charles (unpublished report). We found that blank readings on normal urine gave no turbidity or at most only an opalescence below the threshold value of the calibration curve. The reliable quantitative sensitivity threshold of this method was estimated at 0.1 mg. of chloroquine per 100 ml. of urine.

Results of the Investigation

As usual in Southern Nigeria, the predominant parasite species was *Plasmodium falciparum*, which occurred in all children of the positive selected sample. *P. malariae* in association with *P. falciparum* occurred in 14% of the children. The overall parasite density index was 4.2 and centred around 800–1,600 parasites per c.mm. Gametocytes of *P. falciparum* were present in 17% of cases.

Since it was important for this investigation to determine only the comparative speed of action of the three treatments, the daily blood examinations were not extended beyond the eighth day after beginning the chloroquine administration. The results are shown in the Table.

Disappearance of Parasitaemia in Three Groups of Children After Chloroquine Administration

Group	No.	Percentage Cleared Within 1 Week	Clearance Time in Days. Mean and S.E.	Gametocyte Rate for *P. falciparum* at End of Week
Single dose 300 mg. by mouth	10	100	1·8±0·2	20%
Single dose 300 mg. in one suppository	12	38	2·8±0·4	25%
1,500 mg. in 5 suppositories over 5 days	6	100	3·0±0·06	17%

In two children of the two larger groups fully grown schizonts of *P. malariae* persisted in the blood for two to three days after the *P. falciparum* infection was cleared, but the small number of these cases did not justify the calculation of a specific clearance time for *P. malariae*.

There was no significant change in the gametocyte rate of *P. falciparum* after the last day of examination, at the end of the week. Neither was there any evident correlation between the original parasite density count of individual children and their clearance time.

The comparative rates of excretion of chloroquine in urine, following the administration of a single dose given by mouth or of a single and multiple dose administered per rectum were assessed in 20 children.

It was found that after the oral administration of a single dose of chloroquine sulphate (300 mg. chloroquine base) to six children the mean amount of the base excreted in the urine of each child over eight days was 58.9 ± 4.8 mg., or 19.6% of the administered drug. Of the same amount of chloroquine sulphate (300 mg. base) given as a suppository to each of eight children, the mean recovery in the urine over eight days was 14.6 ± 3.9 mg. per child (4.9% of the administered dose). We have also administered to six children once a day over five days a suppository containing 300 mg. of chloroquine base; the mean amount of the drug recovered in the urine within two weeks after the administration was 82.0 ± 9.2 mg., or 5.5% of the total dose of 1,500 mg.

Clinical Value of Chloroquine Suppositories

The results of this study show that at the single dosage of 300 mg. of base the drug given by mouth is about three times as active as when given in the form of suppositories, the proportions of children cleared of parasites within a week after the drug administration being respectively 100/38, or a ratio of 2.6. The relevant ratio between the urinary excretion of the chloroquine administered as a single dose by the two ways is 4:1 (19.6% against 4.9%) in favour of the peroral treatment.

While a single intrarectal dose of 300 mg. of chloroquine cleared only 38% of the sample of children infected with *P. falciparum*, the multiple administration of 300 mg. of the drug daily for five days cleared all the children of our sample within one week. It appears that the intrarectal absorption of the drug when given in multiple doses is of greater therapeutic value. As pointed out by Canet (1951), when it comes to speed of action the intrarectal administration of chloroquine for treatment of severe malaria cannot compete with the oral, let alone parenteral, administration of the drug. Nevertheless, there might be circumstances when chloroquine suppositories would be of value if the taking of the drug by mouth presented difficulties, as might often be the case in paediatric practice. Vomiting and refusal to swallow the tablet are the most common indications for intrarectal treatment of not too severe malaria, perhaps after a preliminary parenteral loading dose. It is obvious that chloroquine suppositories must be given in much higher dosage than when the drug is given by mouth.

Canet (1951) advised that the intrarectal dose should be approximately twice the oral dosage. With a dose of 750 mg. (to children under 3 years of age) and of 1,350 mg. (to children of a mean age of 7 years) given over three days, Canet noted the disappearance of parasitaemia (*P. falciparum* and *P. vivax*) in all his 40 Vietnamese children. The mean clearance time of his series of *P. falciparum* infections was 2.85 days. The results obtained by us with a smaller sample of slightly older African children, given 1,500 mg. of intrarectal chloroquine over five days, were very similar, the mean clearance time being 3.0 days. Canet thought that the total dosage of chloroquine in suppositories given over five days should be as follows: infants, 750 mg.; 1 to 3 years, 1,050 mg.; 3 to 6 years, 1,800 mg.; 6 to 10 years, 2,400 mg. These dosages are actually more than twice the generally accepted oral dosage (Covell *et al.*, 1953), but, judging from the comparative rates of chloroquine excretion, are perfectly acceptable. In fact, it seems that at times even a higher intrarectal dosage of chloroquine might be justified, especially as side-effects of this treatment have not been recorded and are probably very rare.

A point should be mentioned with regard to the technique of intrarectal administration of chloroquine. The available suppositories are of two strengths—300 and 150 mg. of chloroquine base; they are very well preserved in a plastic strip pack, but have the disadvantage of getting soft in tropical climates and

must be kept on ice before use. This might not always be easy, and it seems that suppositories with a higher melting-point would be desirable for tropical practice.

The French workers believe that chloroquine suppositories might have some use not only for treatment but also for prevention of malaria in infants and small children at a weekly dosage of 150 to 600 mg. (one or two suppositories a week). That this is a possibility cannot be denied, though the value of this method is surely limited to exceptional cases.

Intrarectal chloroquine might be of value in the treatment of amoebiasis, rheumatoid arthritis, and lupus erythematosus.

Urinary Elimination of Chloroquine

Comparing the renal elimination of a single dose of chloroquine given by mouth with that given per rectum, it was of interest to find that the trend of the daily excretion of the drug is similar and that the amount of chloroquine base found in the urine 24 hours after administration decreased in both groups to one-tenth of this value in about six days. The excretion curve of chloroquine after repeated daily administration of five suppositories showed a slight peak on the fourth and fifth days, but maintained its relatively uniform level for one week. The proportion of the total amount of chloroquine excreted within two weeks after five suppositories was slightly higher (5.5%) than in the case of a single dose (4.9%).

It must be made clear that this investigation gives no direct information on the actual chloroquine concentration in the plasma of our patients. Renal excretion of many synthetic antimalarials depends on so many variables (in addition to plasma concentration) that it cannot be used for direct estimation of the amount of the drug in body fluids or tissues.

Haag, Larson, and Schwartz (1943) showed that the amount of quinine eliminated in the urine depends on the acid-base balance of the individual. The Army Malaria Research Unit, Oxford (1945), found that the same is true with regard to mepacrine, and that the excretion of this drug by the kidneys is correlated with the excretion of ammonia and with plasma mepacrine concentration. The latter finding led to an elegant method of indirect calculation of plasma mepacrine levels from two empirical formulae based on the fact that the ratio of urinary mepacrine to urinary ammonia is proportional to the plasma mepacrine concentration.

The influence of the acid-base balance on the urinary elimination of chloroquine was studied by Jailer *et al.* (1947), who found that the daily excretion of the drug averaged 24% of the daily dose. Administration of sodium bicarbonate for three days decreased the mean daily excretion rate of chloroquine to 12.8%, while acidification, using ammonium chloride, increased the rate to an average of 37% of the daily intake.*

In a study of the absorption and excretion of several antimalarial drugs Berliner *et al.* (1948) confirmed these findings, and reported that chloroquine was excreted in faeces in a proportion of 8% of the daily dose of the drug, while under ordinary conditions the urinary excretion averaged 14% of the daily dose (range 10–25%). Berliner and his colleagues found that the metabolic fate of chloroquine varies from man to man, but that generally about 25% of the drug is excreted, while the rest undergoes slow degradation.

In most of the chloroquine estimations carried out by the authors quoted above one or other of the specific and sensitive methods of Brodie *et al.* (1945, 1947) was used. It was therefore of interest that our investigation of the urinary excretion of chloroquine, using a non-specific and admittedly less sensitive turbidimetric method, produced very similar results. The amount of chloroquine base excreted by our first series of children was 19.6% of the administered dose. The relevant figure was 24% as found by Jailer *et al.* (1947), 14% by Berliner *et al.* (1948), and 29% by E. Paulini and R. Soarez (1956, unpublished); while Fuhrmann and Koenig (1955), who used a turbidimetric method, reported that 16.9% of the intake of the drug is excreted in the urine.

*The therapeutic implications of this finding are considerable, especially in cases where the use of high doses of chloroquine is followed by the well-known side-effects of the drug. Administration of acids will speed up the elimination of chloroquine from the body.

Summary

The parasiticidal action of chloroquine sulphate given by mouth was compared with that given per rectum, in suppositories, in three groups of hospitalized African children. It was found that the single intrarectal dose of 300 mg. (base) of the drug cleared only 38% of children of *P. falciparum* schizonts, against 100% when the same dose of chloroquine was given by mouth.

With five repeated daily doses of 300 mg. (base) the action of chloroquine suppositories was complete though slow, with a clearance time of three days.

Chloroquine given by the mouth is far better absorbed and its urinary excretion averages 20% of the total amount of administered drug; the respective figure for intrarectal chloroquine does not exceed 5%.

Chloroquine suppositories cannot replace the more usual methods of administration of this drug, especially when the speed of action is of importance. Nevertheless, they might be used with advantage in some special circumstances, particularly in paediatric practice.

A turbidimetric method of chloroquine assay in urine was used with satisfactory results.

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REFERENCES

Army Malaria Research Unit (1945). *Ann. trop. Med. Parasit.*, **39**, 53.
Berliner, R. W., Earle, D. P., Taggart, J. V., Zubrod, C. G., Welch, W. J., Conan, N. J., Bauman, E., Scudder, S. T., and Shannon, J. A. (1948). *J. clin. Invest.*, **27**, No. 3, Part 2: Symposium on Malaria, p. 98.
Brodie, B. B., and Udenfriend, S. (1945). *J. biol. Chem.*, **158**, 705.
—— —— Dill, W., and Downing, G. (1947). Ibid., **168**, 311.
Bruce-Chwatt, L. J. (1951). *Trans. roy. Soc. trop. Med.*, **44**, 563.
—— and Archibald, H. M. (1953). *Brit. med. J.*, **1**, 539.
—— and Charles, L. J. (1957). Ibid., **2**, 23.
Canet, J. (1951). *Bull. Soc. Path. exot.*, **44**, 481.
Covell, G., Coatney, G. R., Field, J. W., and Singh, J. (1953). *Wld Hlth Org. Monogr. Ser.*, **No. 27**.
Fuhrmann, G. (1950). *Z. Tropenmed. Parasit.*, **2**, 279.
—— and Koenig, K. (1955). Ibid., **6**, 431.
Haag, H. B., Larson, P. S., and Schwartz, J. J. (1943). *J. Pharmacol. exp. Ther.*, **79**, 136.
Jailer, J. W., Rosenfeld, M., and Shannon, J. A. (1947). *J. clin. Invest.*, **26**, 1168.
Lavier, G., and Schneider, J. (1951). XIII Congrès de Pédiatres de Langue Française, Alger, 1951.
Trowell, H. C., and Jelliffe, D. B. (1958). *Diseases of Children in the Subtropics and Tropics*. Arnold, London.