

Pulmonary Edema Due to Fluid Overload in Falciparum Malaria

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OBJECTIVE: To determine whether restriction of intravenous fluid intake would decrease the incidence of pulmonary edema in comatose patients with falciparum malaria.

BACKGROUND: Brooks et al. presented case—histories on five patients with falciparum malaria who developed pulmonary edema and died (1). Four of the patients had received intravenous fluids. Punyagupta et al. described 12 patients with this complication of whom nine died (2). All patients had received intravenous fluids. Both authors claim that the pulmonary edema was not due to fluid overload but to a specific complication of the disease.

This paper reports on six comatose adult patients with falciparum malaria who developed pulmonary edema which was attributed to excessive intravenous fluid therapy. Ten other comatose patients with falciparum malaria, studied later, did not develop pulmonary edema and this was attributed to optimal intravenous fluid therapy.

DESCRIPTION: The study was carried out at the Trad Provincial Hospital in Southeastern Thailand 400 km from Bangkok. The area is endemic for chloroquine—resistant falciparum malaria (3, 4). Diagnostic services and nursing facilities were limited at the time of the study (1973—1974). Study physicians maintained detailed clinical records, closely monitored intravenous fluid therapy and, in most patients, recorded the approximate urine output. The patients were seriously ill on admission and there was no facility for weighing them in bed before treatment. Central venous pressures (CVP) could not be monitored.

Initially eight comatose patients (six adults, two children) with falciparum malaria and pulmonary edema were studied. Not all patients were under the direct care of the research physicians. Following the restriction of intravenous fluid intake as a change in therapeutic policy, 10 comatose adults with falciparum malaria were studied who did not develop pulmonary edema. The two groups were equivalent with respect to clinical severity and average parasite densities.

Quantitative parasite counts (5) were determined at least twice daily in hospital and at follow—up examinations on days 14, 21 and 28 and often later. Hematocrits and white blood cell counts were performed regularly. Sera were collected and taken to the SEATO Laboratory in Bangkok for determination of quinine concentrations (6). There were no facilities at Trad for radiography or autopsies.

PROGRESS: In six comatose adults the onset of pulmonary edema was apparently related to intravenous fluid therapy (Table 1). These patients received an average of 1,767 ml intravenous fluid during the first eight hours after admission and altogether 2,825 ml in the first 24 hours. The physical signs of pulmonary edema developed following intravenous therapy. In all six patients, fluid intake greatly exceeded urine output during the period that pulmonary edema developed. In three patients, coma developed or worsened after intravenous fluids.

Ten comatose adult patients studied later did not develop pulmonary edema. Their average fluid intake was 563 ml in the first eight hours and 1,181 ml in the first 24 hours (Table 2). The differences between the eight hour inputs ($t = 4.2, p < 0.001$) and 24 hour inputs ($t = 4.1, p < 0.001$) were statistically significant. No clinical deterioration followed intravenous therapy in the second group.

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The case—histories on two adults and two children are now given who were not under the care of physicians from SEATO Medical Research Laboratory.

Case No. 2: This 30 year old woman was six months pregnant. She had become comatose on the day of admission. On examination the lung—fields were clear. Her temperature was 38.8°C and her asexual parasite density of *P. falciparum* was 94,600 per cu.mm. Since she was pregnant, quinine was not prescribed for fear of abortion. One thousand milliliters of five per cent dextrose with 200 mg chloroquine base was infused in one hour. A second similar unit was infused in the following six hours. Thus within eight hours of admission the patient had received 2,000 ml fluid. The patient developed noisy breathing. Loud moist crepitations were present throughout both lung—fields. Since her *falciparum* malaria was deemed resistant to chloroquine, a third liter with 1,000 mg quinine was now administered. The next morning she awoke briefly but lapsed into coma following further intravenous fluids which were administered at the rate of 1,000 ml every eight hours. The physical signs of gross pulmonary edema persisted and she died 24 hours later at which times the parasite count had decreased to 60 per cu.mm.

Case No. 6: This 18 year old man had been ill for eight days and aphasic for two days. The patient had been taken to an unlicensed practitioner on the day before admission. Four thousand milliliters of intravenous fluid were infused by the practitioner over a 12 hour interval. After 3,000 ml, the patient was able to walk to the toilet (according to his brother). Another 1,000 ml was rapidly infused and the patient went into a deep coma from which he never recovered. He was brought into the hospital moribund about 10 hours later, coughing up blood—tinged sputum. He had cyanosis and was breathing noisily. Extensive moist râles were heard. The *P. falciparum* density was 130,000 per cu.mm. In hospital he received quinine 500 mg in 500 ml normal saline intravenously over a four hour interval. The diuretic, furosemide 20 mg, was administered intravenously and urine output was 800 ml during the next 12 hours. A second quinine infusion was begun 16 hours after admission. The total fluid input in hospital was 700 ml and output 1,300 ml, but the physical signs and gross pulmonary edema worsened. The patient deteriorated and died 22 hours after admission.

Case No 17: This four year old boy weighed 10 kg. On admission at 1100 hours he was stuporous with enlarged liver and spleen. The *P. falciparum* density was 273,000 per cu.mm. Quinine 250 mg in 500 ml five per cent dextrose in half—normal saline was infused over five hours. His condition deteriorated and signs of pulmonary edema supervened. On the next day he was in coma and extensive bubbly râles were heard over both lung—fields. The parasite count had decreased to 48,000 per cu.mm. Another 250 mg quinine in 500 ml was infused in eight hours. After two hours his coma had deepened and spleen had become larger. Convulsions appeared, which were only partly responsive to Nembutal intramuscularly and intravenously. He developed an extension spasm of the neck. On the next day his parasite count had decreased to 10,000 per cu.mm. The physical signs of severe pulmonary edema persisted. Another 250 mg quinine in 500 ml was infused during the day and the parasite count decreased to 2,000 per cu.mm. The boy was moribund and his father took him home to die.

Comment: In this 10 kg boy, an initial 500 ml infusion appeared to precipitate pulmonary edema.

Case No. 18: This five year old girl weighing 12 kg was admitted seriously ill but fully alert. Her asexual count of *P. falciparum* was 396,000 per cu.mm. Quinine 250 mg in 250 ml normal saline was infused over 90 minutes. Her lungs remained clear at the end of the infusion. On the next morning, 17 hours after admission, her condition appeared to have improved. The parasite count had decreased to 54,000 per cu.mm. Another 250 mg quinine was infused in 500 ml and she developed fits and went into coma. Extensive râles were audible throughout both lung—fields. Twenty—four hours later another infusion of 500 ml quinine was given. She continued to deteriorate with the clinical signs of coma and gross pulmonary edema and died.

Comment: In this 12 kg girl, an initial infusion of 250 ml was uneventful but a subsequent infusion of 500 ml precipitated a fatal pulmonary edema.

OPTIMAL INTRAVENOUS HYDRATION: As described above, pulmonary edema developed in eight patients (six adults, two children) following intravenous fluid. Therefore in subsequent patients fluid input was restricted.

The patients were in coma on admission or lapsed into coma shortly afterwards. None developed pulmonary edema and this was attributed to the deliberate restriction of intravenous therapy (Table 2). A positive fluid balance was not detected in any patients. The following case description is representative.

Case No. 12: This 26 year old man weighed 45 kg and was admitted in coma. His initial asexual count of *P. falciparum* was 10,800 per cu.mm. which cleared within 64 hours. Intravenous fluid intake over the first four days was 1,000, 1,000, 1,450 and 1,000 ml, respectively. On this restricted fluid intake his urine output was about 1,000 ml daily, indicating that fluid balance was neutral. The intravenous quinine input over the first four days was 1,000, 0, 500 and 0 mg, respectively. Coma persisted 87 hours and he made an uneventful recovery. The patient's recovery was partly attributed to the moderate doses of both intravenous fluids and quinine. This treatment was successful with cases 7, 8 and 13-16 in particular.

QUININE DOSAGE: Detailed records of quinine therapy were available on four of the six patients who developed pulmonary edema. These men received on average 1,500 mg quinine base intravenously in the first 24 hours (Table 3). The 10 patients who did not develop pulmonary edema received on average 1,055 mg (Table 4). The difference is statistically significant ($t = 5.1$, $p < 0.001$); however, there was no evidence that quinine caused pulmonary edema. For example, Case No. 10 was admitted in deep coma and apparently moribund. He received 1,500 mg quinine intravenously in 1,500 ml daily for the first two days. A toxic concentration of serum quinine was produced (14.1 mg/L) but there was no evidence of pulmonary edema. Case No. 11 also received 1,500 mg of quinine daily intravenously and his cerebral state appeared to deteriorate after each dose of quinine, but intravenous fluids were restricted to 1,500 ml daily and pulmonary edema did not develop. Similarly Case No. 12 was overdosed with quinine since the serum quinine concentration rose to 20.6 mg/L. Pulmonary edema did not develop but the quinine appeared to precipitate aphasia and coma.

DISCUSSION: There are three lines of evidence that pulmonary edema in falciparum malaria is usually caused by therapy and not by the disease.

Firstly, fatal pulmonary edema (or acute pulmonary insufficiency) is rarely mentioned in the older literature but has only recently emerged as a serious and challenging complication of acute falciparum malaria (2). If pulmonary edema were frequently an integral part of the disease then it should appear prominently throughout the literature. However, some textbooks do not mention pulmonary edema (7, 8) and, in another, only one case is mentioned (9). This is in marked contrast to the extensive descriptions of cerebral and other complications. Pulmonary edema has emerged as a clinical problem in the disease coincidentally with the extensive use of intravenous fluids.

Secondly, 80 per cent (21/26) of recent cases of pulmonary edema described in this and other studies (1, 2, 10, 11) developed after admission to hospital. At least one other patient had received intravenous fluids before admission. This suggests that some cases are due to therapy.

Thirdly, in most patients who develop pulmonary edema, there is evidence of a high fluid intake or a positive fluid balance. A positive fluid balance did not occur in our successfully managed patients. It was striking how often the urine output matched the restricted intravenous fluid intake. Either insensible loss is an overrated factor in falciparum malaria or water is produced by tissue catabolism in the disease.

Our adult Thai patients who developed pulmonary edema received an average of 1,800 ml fluid intravenously in the first eight hours after admission and altogether an average of 2,800 ml in the first 24 hours. The patients who did not develop pulmonary edema received an average of 560 ml in the first eight hours and 1,180 ml in the first 24 hours.

Similarly, in Vietnam, pulmonary edema did not develop in any of 73 patients with recrudescing falciparum malaria who received 1,500 ml of intravenous fluid daily (12). These data suggest that re-interpretation of some recent studies is indicated.

In their first paper Punyagupta et al. described two patients. In Case No. 1, the fluid input in the first four days was 17,855 ml and the output was 8,850 ml, giving a positive fluid balance of 9,000 ml, which the authors did not discuss; but during this time the patient developed pulmonary edema. Between the fifth and seventh days the fluid intake was 7,585 ml and output 11,550 ml, giving a negative balance of 3,965 ml. During this time diuretic therapy and many other drugs were given and the pulmonary edema resolved. During the seven days of observation, the average daily fluid intake was 3,634 ml and output of urine was 2,914 ml, which is very high. It should be remembered that homeostasis can be achieved with as little as 500 ml urine daily (14).

In the second patient, pulmonary edema developed on the second hospital day during which the fluid intake was 4,750 ml and output 1,950 ml. Although the diuretic furosemide was administered to both patients, the authors attributed survival to the treatment with heparin, dexamethasone, dextran and antimalarial drugs. These two patients were included in the total of 12 described in the second report (2). They claimed that fluid overload did not occur, and preferred the term acute pulmonary insufficiency; but they gave no information on fluid balance in their other 10 cases.

Brooks et al. described fatal pulmonary edema in five patients of whom four developed the complication between the third and tenth hospital days (1). In these four patients the average daily fluid intake was 2,900 ml and output 1,800 ml, giving an average positive fluid balance of 1,100 ml daily. Their fifth patient did not receive intravenous fluid before the onset of pulmonary edema and fluid overload was presumably not a factor in that patient.

In three of our patients and probably in many others described in other reports, fluid overload appeared to cause both pulmonary edema and coma (e.g., cerebral edema).

Dehydration is either a rare or non-existent feature of falciparum malaria. Metabolic studies have demonstrated hyponatremia, an increased plasma volume but no abnormality of total body water in many patients with acute falciparum malaria (25, 16). Thus, it is surprising that having demonstrated an increased plasma volume in falciparum malaria, Brooks et al, dismissed fluid overload as being a factor in their patients with pulmonary edema (1).

Miller et al. confirmed the hyponatremia, considered that the cause was salt depletion and water retention and said "serious errors in treatment can arise from the blanket assumption that all malaria patients are dehydrated and routinely in need of intravenous water and electrolytes. In those with severe anemia and cardiac disease this could precipitate pulmonary edema" (17). This viewpoint had been expressed before (18). Tigertt (personal communication) has confirmed that many instances of pulmonary edema among U.S. troops with falciparum malaria in Vietnam were due to fluid overload. In retrospect most patients (U.S. military in Vietnam) with edema in falciparum malaria had a progressive weight gain before the onset of dyspnea in contrast to the usual weight loss of 1.7 to 2.6 kg in the disease (19).

There is evidence, therefore, that in falciparum malaria fluid overload can be produced by intravenous fluid therapy. Extreme thirst is a frequent symptom in the disease, which raises the question whether excessive oral intake of fluids could sometimes precipitate pulmonary edema and coma.

The central venous pressure (CVP) has been normal when measured in falciparum patients with pulmonary edema (1, 2, 11). Our interpretation would be that fluid overload can precipitate pulmonary edema without increasing the CVP. Damage to the pulmonary tissues is probably common in falciparum malaria; thus, pulmonary edema will occur more readily than in healthy lungs.

Since fluid restriction is important in falciparum malaria, the indications for intravenous therapy need to be clearly defined. Inadequate oral intake is obviously an indication. As a minimum, intravenous fluids

are needed to prevent oliguria (urine output less than 400 ml daily) and as a vehicle when intravenous quinine therapy is needed.

Some cases of pulmonary edema or acute pulmonary insufficiency in falciparum malaria are probably due to the disease and are not related to therapy. Deaton reported two patients in whom respiratory symptoms occurred before treatment (11). Fluid balance was negative in one patient and slightly positive in the other.

There is evidence for several pulmonary lesions in falciparum malaria (Table 5). Non-fatal bronchitis or pneumonia is often mentioned in the older literature (20, 21). Clinically diagnosed pulmonary edema, which can resolve with therapy, has been discussed in this paper. Pulmonary edema is a terminal event detected at autopsy in some patients dying of cerebral malaria or other complications of the disease (22).

Most patients with malaria are admitted to remote hospitals. We found in a remote hospital (without facilities for CVP and detailed body weights and urine outputs) that the restriction of fluid intake greatly reduced the incidence of pulmonary edema. This finding is especially applicable to other remote hospitals where fluid intake can be regulated but CVP, body weight and urine output cannot always be determined.

CONCLUSIONS: Pulmonary edema in falciparum malaria may be caused by excessive fluid intake. The present study has shown that the incidence of pulmonary edema can be greatly reduced if fluid input is restricted. One thousand five hundred milliliters of fluid daily (including blood transfusions) or 500 ml every eight hours is the maximum safe intake in full-sized adults. In smaller adults (e.g. many Thais), 1,000 ml is the optimum daily intake. Children should receive proportionately smaller volumes. A positive fluid balance should be avoided if urine output is adequate (e.g., about 1,000 ml urine daily in adults). It is wise to avoid intravenous therapy at night when nursing supervision may be limited.

If pulmonary edema occurs, diuretic therapy is logical: e.g., furosemide by slow intravenous injection. Quinine therapy must also be restricted to prevent toxicity and 1,000 mg daily (two doses) is usually sufficient in adults.

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Table 1. Patients with Falciparum Malaria and Coma. Development of Pulmonary Edema Attributed to Intravenous Overhydration

Patient Number	Age (years)	Maximum Asexual Parasite Count (per cu.mm.)	Volume Infused (ml)			
			0-8 Hrs.	8-16 Hrs.	16-24 Hrs.	Total 0-24 Hrs.
1	20	317800	1450	0	1000	2450
2*	30	94600	2000	0	1000	3000
3	30	639600	1650	350	1000	3000
4	16	96500	1500	0	500	2000
5*	22	777600	1000	500	500	2000
6*	18	103600	3000	1000	500	4500
Average	23	338300	1767	308	750	2825

* Fatal cases

Table 2. Patients with Falciparum Malaria and Coma. Absence of Pulmonary Edema Attributed to Optimal Intravenous Hydration

Patient Number	Age (years)	Maximum Asexual Parasite Count (per cu.mm.)	Volume Infused (ml)			
			0-8 Hrs.	8-16 Hrs.	16-24 Hrs.	Total 0-24 Hrs.
7	35	719800	1000	0	1000	2000
8	16	6300	900	100	0	1000
9	30	307600	630	370	500	1500
10*	45	131200	500	500	500	1500
11	24	772600	500	500	500	1500
12	26	10800	500	0	500	1000
13	42	836200	500	0	500	1000
14	14	12800	350	460	0	810
15	53	2000	500	0	250	750
16	14	72300	250	0	500	750
Average	30	287200	563**	193	425	1181**

* Fatal case

** Significantly less ($p < 0.01$) than the input in the patients who developed pulmonary edema (See Table 1).

Table 3. Patients with Falciparum Malaria, Coma and Pulmonary Edema Intravenous Quinine Dosage First 24 Hours

Patient Number	Quinine Infused (mg)				Comment
	0-8 Hrs.	8-16 Hrs.	16-24 Hrs.	Total 0-24 Hrs.	
1	1000	0	500	1500	Mostly chloroquine therapy
2					
3	850	150	500	1500	
4	1000	0	500	1500	
5	1000	0	500	1500	
6	?	?	(500)	?	Treatment before admission
Average	963	37	500	1500	

Table 4. Patients with Falciparum Malaria and Coma but without Pulmonary Edema
Quinine Dosage First 24 Hours

Patient Number	Quinine Infused (mg)				Comment
	0-8 Hrs.	8-16 Hrs.	16-24 Hrs.	Total 0-24 Hrs.	
7	500	0	500	1000*	Died Quinine toxicity Quinine toxicity
8	950	50	0	1000*	
9	650	350	500	1500	
10	500	0	750	1250	
11	500	500	500	1500	
12	500	0	500	1000*	
13	500	0	500	1000	
14	350	450	0	800*	
15	500	0	250	750*	
16	500	0	250	750*	
Average	545	135	375	1055	

* Modest amounts of quinine and intravenous fluids were associated with an optimal clinical response in these patients.

Table 5. Pulmonary Lesions in Falciparum Malaria

Lesion	Causation	Comment
1. Pneumonitis	Disease	Non-fatal
2. Bronchitis	Disease	Non-fatal
3. Pulmonary edema	Therapy	Fatal or reversible
4. Pulmonary edema or "acute pulmonary insufficiency"	Disease	Fatal (diagnosed before death)
5. Pulmonary edema	Disease	Autopsy finding