Augmentation of Frusemide Diuresis by Morphine in High Altitude Pulmonary Oedema

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We have already reported that anxiety, restlessness, and laboured breathing associated with high altitude pulmonary oedema, which did not respond satisfactorily to oxygen therapy, were found to respond dramatically to intravenous morphine (Singh *et al.*, 1965). Subsequently, haemodynamic studies in convalescents from high altitude pulmonary oedema suggested that the beneficial effect of intravenous morphine might partly result from reduction of the pulmonary blood volume due to redistribution of blood in the periphery (Roy *et al.*, 1965).

We now report that morphine also augments frusemide diuresis in high altitude pulmonary oedema and accelerates recovery. The probable mechanisms are discussed.

SUBJECTS AND METHOD

There were 98 men, 18 to 38 years old, all plainmen, of whom 22 were new arrivals at high altitude; 76 had been resident at high altitude for 4 to 17 months, and developed acute pulmonary oedema on their return to high altitude after a sojourn in the plains of 60 to 70 days; none had suffered from pulmonary oedema during their first trip to high altitude. Both new arrivals and former residents developed acute pulmonary oedema 24 to 96 hours after arrival at high altitude. The vulnerable altitude was 11,500 feet. There were 69 out of 98 who were also suffering from acute mountain sickness.

All cases were treated locally at the same altitude (11,500 feet). Immediately on arrival at hospital, a pre-treatment clinical and radiological examination of the chest was made, and was repeated every 24 hours until the chest was clear.

The trial, which was controlled but not blind, then started. Treatment A was administered to 84, and Treatment B, to 14 from a random selection. Treatment A consisted of a single injection of morphine 15 mg. intravenously and frusemide 20 mg. intravenously every 12 hours on the first day, and frusemide 40 mg. orally every 12 hours on the second and third days. Treatment B consisted of Treatment A minus morphine.

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The patients remained in bed in the same environment throughout these three days.

During this period fluid intake consisted of hot sweetened tea and milk from a fixed ration, and additional quantities of water as required. The caloric value (1200 calories) and sodium content (552 mg.) were constant for all patients. The intake of water could not be fixed on account of mountain sickness in the majority of cases.

Urine collections were done under supervision and were carefully measured to the millilitre. The difference between the urinary output and the intake of fluid in ml. constituted the effective diuresis.

More than one consideration, based on our previous experience, weighed with us in restricting the number in the control group on Treatment B. (1) Most of the cases of high altitude pulmonary oedema occurred under field conditions and were severe. Anxiety, restlessness, and laboured breathing, which had not responded to bed-rest and oxygen therapy, had been specifically relieved with morphine. When morphine was not used, or was used with restraint, there was an associated mortality. (2) We were not convinced that the slow acting diuretic mersalyl used alone had been of much benefit in provoking a diuresis. We were, however, prepared to take a reasonable risk with frusemide, which is a more rapidly acting diuretic than mersalyl, and forego morphine in a few cases. The unequal numbers, however, do not affect the validity of the statistical test used.

Since the conditions of the experiments, namely the vulnerable altitude at which pulmonary oedema occurred, the location of treatment at the same height, bed-rest, oxygen therapy, and composition, caloric value, and sodium content of the diet, were identical for the two groups, any difference in response was considered to be the result of the morphine component in Treatment A.

RESULTS

Table I gives the statistical analysis of the average effective diuresis obtained on the first, second, and third days in new arrivals and in former residents with Treatment A and with Treatment B. Individual responses are shown by the histograms of the effective diuresis on each day in Fig. 1 and for all the three days in Fig. 2.

TABLE I
EFFECTIVE DIURESIS IN NEW ARRIVALS AND FORMER RESIDENTS
OBTAINED WITH TREATMENT A AND TREATMENT B

	New arrivals				Former residents			
	Treat- ment A	Treat- ment B	Difference	t	Treat- ment A	Treat- ment B	Difference	t
No. of patients	16	6			68	8		
Average diuresis (ml.)								
First day	1276	250	1026	36.47*	1046	803	243	3.82*
Second day	983	155	828	32.18*	941	546	395	9.86*
Third day	613	156	457	15.53*	571	316	255	8.52*
Total for 3 days	2872	561	2311	16.55*	2558	1665	893	11.13*

* Indicates significance at 1 per cent level.

Table II gives the statistical analysis of the average effective diuresis obtained on the first, second, and third days with Treatment A and Treatment B in new arrivals and former residents.

Table III gives the number of new arrivals and former residents clinically and radiologically cleared of high-altitude pulmonary oedema by the first, second, and third day with Treatment A and with Treatment B.

The differences in response among subjects diminished with the passage of days. The differences were more pronounced on the first day and were less on the second and third days (Fig. 1).

The response to Treatment B was greater in the former residents than in the new arrivals, but the difference became smaller on successive days, till on the third day, it was only slight (Fig. 1).

The difference in response to Treatment A and Treatment B was highly significant in all cases (Table I), and was apparent in Fig. 1 and Fig. 2.

The difference between the response of new arrivals and the response of former residents to Treatment A was significant only on the first day when morphine was used. The results for the second and third days did not show significant differences (Table II).

The difference in response between new arrivals and former residents to Treatment B was significant on all three days (Table II).

Complete clinical and radiological clearance of the lungs was obtained within three days in all the cases (Table III). With Treatment A the effect was obtained earlier, within a day in some cases and within 2 days in most of them. The percentage of cases

FIG. 1.—Histogram of the effective diuresis obtained on first, second, and third days in new arrivals and in former residents with Treatment A and with Treatment B.

cured within 48 hours was significantly higher with Treatment A, both for new arrivals and former residents, than with Treatment B.

No patient deteriorated during the course of treatment, and after initial alleviation of anxiety, restlessness, and laboured breathing with morphine, there was no recurrence of these symptoms. A notable feature was that both pulmonary oedema and acute mountain sickness were benefited more or less simultaneously in each case.

DISCUSSION

We have earlier recorded that in a few cases of high altitude pulmonary oedema the first symptoms were frequency of micturition and oliguria (Singh *et al.*, 1965). Subsequent observations have shown that after arrival at high altitude, oliguria with either frequency or infrequency of micturition, invariably precedes high altitude pulmonary oedema in both new arrivals and former residents. In contrast, healthy controls under identical circumstances usually have a normal output of urine or polyuria. With the onset of pulmonary oedema anti-diuresis persists.

When the pituitary-adrenal system is activated by stress both vasopressin and adrenal steroids are released, and the balance between them determines whether an individual will have oliguria or polyuria. For example, patients undergoing severe stress, with demonstrably increased adrenal cortical activity, are

FIG. 2.—Histogram of the total effective diuresis obtained on all three days in new arrivals and in former residents with Treatment A and with Treatment B.

TABLE II
EFFECTIVE DIURESIS OBTAINED WITH TREATMENT A AND TREATMENT B
IN NEW ARRIVALS AND FORMER RESIDENTS

	Treatment A			Treatment B		
	New arrivals	Former residents	t	New arrivals	Former residents	t
No. of patients	16	68		6	8	
Average diuresis (ml.)						
First day	1276	1046	5.07*	250	803	13.73*
Second day	983	941	1.46	155	546	27.02*
Third day	613	573	1.79	156	316	9.29*
Total for 3 days	2872	2560	5.36*	561	1665	23.93*

* Indicates significance at 1 per cent level.

TABLE III
NUMBER OF NEW ARRIVALS AND FORMER RESIDENTS CLINICALLY AND RADIOLOGICALLY CLEARED OF HIGH ALTITUDE PULMONARY OEDEMA BY FIRST, SECOND, AND THIRD DAY OF TREATMENT A AND TREATMENT B

	New arrivals						Former residents					
	Treatment A			Treatment B			Treatment A			Treatment B		
Days of treatment	1	2	3	1	2	3	1	2	3	1	2	3
No. of cases radiologically and clinically cured (total 98)	2	10	4	Nil	1	5	6	50	12	Nil	3	5

frequently observed to excrete large volumes of relatively dilute urine even when dehydrated. This occurs despite marked increase of anti-diuretic hormone in the plasma and urine and there is but slight response to administered anti-diuretic hormone. These findings suggest that its renal action is antagonized, probably by adrenal steroids (Williams, 1955). By analogy in these cases, it may be concluded that anti-diuresis in impending cases of high altitude pulmonary oedema results from excess of the hormone, or deficiency of adrenal steroids, or both. There is a possibility that people predisposed to high altitude pulmonary oedema hypoventilate after arrival at high altitude and that this hampers the inhibition of anti-diuretic hormone. Normally, hyperpnoea due to hypoxia causes polyuria. Under these circumstances the intrathoracic blood volume is increased and anti-diuretic hormone inhibition is reflexly induced by stimulation of stretch receptors which are located predominantly in the left atrial wall and are sensitive to an increase in the central blood volume (Henry, Gauer, and Reeves, 1956; Gauer, Henry, and Sieker, 1961).

Morphine has long been known clinically to inhibit water diuresis (Fee, 1929; Master, 1941; Ferrer and Sokoloff, 1947). The effect is, however, not operative in all patients, cardiac or otherwise. Hopmann (1928), for instance, said that morphine was a diuretic in his cardiac cases. This apparent paradox depends on the ability of morphine to stimulate as well as depress the release of corticotrophin. There is release of corticotrophin as long as depression does not occur and sensory impulses are intact (Krueger, Eddy, and Sumwalt, 1941; Briggs and Munson, 1955). Conditions conducive to increased corticotrophin secretion and improvement of respiration appear to have obtained during our therapy of high altitude pulmonary oedema with morphine. Thus, given intravenously, morphine produced a dramatic alleviation of anxiety, restlessness, and laboured breathing without evidence of any depressive effect; breathing returned to normal and only mild sleep or drowsiness was induced (Singh *et al.*, 1965).

With the onset of pulmonary oedema, anti-diuresis may be further aggravated by increasing hypoxia and reduced splanchnic flow which are likely to follow. Neurogenic vasoconstriction of the renal vessels is known to occur when the arterial oxygen saturation falls below 50 per cent (Gregg and Thurau, 1961). The pulmonary vascular bed constitutes a low pressure distensible system and a minute increase in the pulmonary venous pressure results in a sizeable accumulation of blood in the lungs. In convalescents from high altitude pulmonary oedema, the pulmonary blood volume has been found to be increased

for several weeks (Roy *et al.*, 1965). It is probable that during oedema this increase is considerable and adversely affects the splanchnic flow.

Morphine may, however, help to neutralize these adverse effects by improving oxygenation of the blood, reducing demands for oxygen, and increasing the splanchnic flow as follows. (1) In laboured breathing there is considerable negativity of intrathoracic pressures; this causes alveolar blood vessels to collapse, thus impeding oxygenation of blood, which morphine abolishes by restoring normal breathing. (2) Morphine allays anxiety, restlessness, and laboured breathing, and diminishes the work load of the ventricles (see below), which has an oxygen-sparing effect. (3) In convalescents from high altitude pulmonary oedema the immediate haemodynamic response to intracardiac morphine is a reduction in the pulmonary blood volume, cardiac output, stroke index, systemic arterial pressure, and filling pressures and work load of both the ventricles (Roy *et al.*, 1965). The same probably happens in high altitude pulmonary oedema, and the shift of blood from the pulmonary circuit elsewhere may help to improve the splanchnic flow.

When frusemide 40 mg. is injected intravenously, diuresis begins within 5 minutes, reaches its peak in 30 minutes, and is almost complete in 90 minutes (Berman and Ebrahimi, 1965). This coincides narrowly with the action of morphine on pulmonary blood volume (see above), reduction of which takes place within 15 minutes. Coincident onset of action of both drugs is probably partly responsible for a greater diuresis with Treatment A.

The greater diuresis in new arrivals in comparison with former residents with Treatment A on the first day is apparently associated with a greater degree of pretreatment anti-diuresis in the new arrivals. The greater degree of diuresis in former residents than in new arrivals on all three days of Treatment B probably results from hypervolaemia in former residents.

Our initial observations indicate that anti-diuresis on arrival at high altitude is also a feature of acute mountain sickness, and its relief during treatment of high altitude pulmonary oedema was probably due to the diuresis induced by the treatment.

SUMMARY

It was found that 22 new arrivals and 76 former residents, 18 to 38 years old, developed pulmonary oedema 24 to 96 hours after arrival at an altitude of 11,500 feet. Of these, 69 also suffered from acute mountain sickness. 84 were treated with a single injection of morphine 15 mg. intravenously and frusemide 20 mg. intravenously every 12 hours on the first day, and 40 mg. by the oral route every 12

hours on the second and third days. Fourteen were treated with frusemide alone in the same dosage.

Under identical experimental conditions treatment with morphine and frusemide was significantly superior to treatment with frusemide alone, and resulted in a greater diuresis and quicker recovery period in all cases.

The response to morphine and frusemide was greater in new arrivals than in former residents only on the first day when morphine was used. The response to frusemide alone was greater in former residents than in new arrivals on all three days. The differences in response among subjects diminished with the passage of days. The differences were more pronounced on the first day and less on the second and third days.

Acute mountain sickness was relieved more or less simultaneously with pulmonary oedema in each case.

The probable modes of action of morphine in enhancing diuresis in high altitude pulmonary oedema are discussed.

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